

Lower Instantaneous Entropy of Heartbeat Dynamics During Seizures in Untreated Temporal Lobe Epilepsy

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Abstract

Temporal lobe epilepsy (TLE) is associated with dysfunction of the autonomic nervous system. While it is known that heart rate variability (HRV) changes in epilepsy comprise both ictal (CRI) and interictal (INT) autonomic cardiac effects, the mechanisms leading to these alterations are not well understood. In this paper we investigate the alterations in instantaneous autonomic complexity during CRI in untreated TLE using bipolar ECG recordings from 10 patients with at least one seizure originating from temporal regions as recorded by video-EEG monitoring. We isolated artifact-free INT and CRI periods and computed mean values of instantaneous point-process Approximate and Sample Entropy (ipApEn and ipSampEn, respectively). ipApEn was significantly lower ($p < 0.02$) and ipSampEn was lower ($p < 0.065$) in CRI vs. INT. The variability (median absolute deviation) of ipApEn was also significantly lower ($p < 0.03$) in CRI vs INT. Our results suggest that ictal events in untreated TLE are associated with a decrease in heartbeat complexity and its variability, possibly pointing toward subtle autonomic changes which may accompany or precede seizures, and can only be detected using an instantaneous, time resolved approach to quantifying autonomic complexity.

1. Introduction

Heart Rate Variability (HRV) changes in epilepsy comprise both ictal and interictal autonomic cardiac effects [1-3]. Interictal autonomic disorders include combined inhibition [2, 4, 5] or suppression [6] of both sympathetic and parasympathetic tone, suppression of the sympathetic or parasympathetic tone, low parasympathetic and high sympathetic tone [7, 8]. The mechanisms leading to autonomic alterations and cardiac

changes in epilepsy are not yet well understood. Some authors have hypothesized an activation of the central autonomic network (CAN), mainly involving the insular cortex and temporal-mesial structures, induced by the spread of repetitive seizures discharges [9, 10].

Recently, reduced HRV, which is consistently related to arrhythmias and increased cardiovascular risk, has been associated with sudden unexpected death in epilepsy patients (SUDEP) in refractory temporal lobe epilepsy (TLE) [11, 12]. While it has been widely accepted that the quantification of ANS complexity can provide useful information on psychophysiological and pathological states [13-19], to date, little is known about ictal HRV changes in untreated patients with newly diagnosed TLE. We have previously demonstrated how the stability and complexity of autonomic dynamics is altered in PD patients when compared to healthy controls [13]. In this study, we hypothesized that the complex behavior of Autonomic Nervous System (ANS) activity is altered in patients suffering from TLE.

We investigate ANS dynamics through analysis of HRV series, employing a recently proposed definitions of approximate and sample entropy based on the inhomogeneous point-process theory: the inhomogeneous point-process approximate and sample entropy (ipApEn and ipSampEn, respectively) [15]. To this end, the unevenly sampled RR interval series is modeled through probability density functions, which characterize and predict the time until the next ventricular event occurs as a function of the past history. Within this framework, Laguerre expansions of the Wiener-Volterra autoregressive terms account for long-term nonlinear information. As the proposed measures of entropy are instantaneously defined through probability functions, these novel indices are able to provide instantaneous tracking of complexity [15, 18], and are not seriously

affected by the stochastic components (noise) underlying physiological dynamics.

2. Materials and Methods

2.1. Point-Process Nonlinear Modeling of Heartbeat Dynamics

We assume history dependence and an inverse Gaussian probability distribution of the waiting time indicating the probability of having an event at time t given that a previous event has occurred. The mean of the probability function $\mu_{RR}(t)$ can be interpreted as signifying the most probable moment when the next event could occur [15, 16, 18], with $\sigma_{RR}(t)$ is the standard deviation. In order to compute the ipApEn and ipSampEn indices, which are described in the next paragraph, we apply a specific model formulation based on a Nonlinear Autoregressive Model with Laguerre expansions (NARL) [15, 16, 18]. Of note, we process the derivative R-R series to improve on the achievement of stationarity within the sliding time window W (in this study $W=90$ s.) [15, 16, 18]. As major advantage, the Laguerre filtering allows for a parsimonious number of unknown parameters that need be estimated, and the implementation of a nonlinear autoregressive Volterra-Wiener model with degree of nonlinearity 2 and long-term memory [15, 16, 18]. Since $\mu_{RR}(t)$ is defined in continuous time, it is possible to obtain instantaneous estimates at an arbitrarily fine timescale, requiring no interpolation between the arrival times of two beats.

Given a time-varying local observation interval of duration W , we find the unknown time-varying parameter vector that maximizes the local log-likelihood through the well-known Newton-Raphson procedure [15, 16, 18]. The model and all its parameters are recursively updated at each iteration without priors. We determine the optimal model order based on the model goodness-of-fit (obtained by prefitting the model to a subset of the data), which is based on the Kolmogorov-Smirnov (KS) test and associated KS statistics [15, 16, 18]. Autocorrelation plots are also considered to test the independence of the model-transformed interval [15, 16, 18]. Once the order is determined, the initial NARL coefficients are estimated by the method of least squares [16].

2.2. The Inhomogeneous Point-Process Entropy Measures

While traditional algorithms estimating measures of entropy provide a single value (or a set of values) within a predetermined time window, in this study we use a new recently introduced definition of approximate and sample entropy as instantaneous entropy measures of the discrete

cardiovascular system complexity. The originality of the new definition relies in the fact that they are fully embedded in the probabilistic framework of the inhomogeneous point-process theory and introduce important differences on the mathematical formulation of the phase-space vectors and on the definition of the distance between phase-space vectors.

In the mathematical formulation, m and $r(t)$ are the embedding dimension and time delay of the phase space, respectively, that are as $r(t) = 0.2\sigma_{RR}(t)$ and $m=2$ [15]. According to the point-process theory, the ipApEn and ipSampEn measures take advantage by defining the vector distance in the phase space as the KS distance (i.e. the maximum value of the absolute difference between two cumulative distribution functions) between two Inverse Gaussian (IG) probability density function, for each pair of vectors [15]. Then, the standard ApEn and SampEn algorithm are considered for the final calculation [15].

As the definition of the proposed entropy measure is fully embedded into the inhomogeneous point-process nonlinear framework, it is possible to obtain instantaneous tracking of the system's complexity as *ipApEn*. Of note, the definition of the is slightly different [15]. Here we also mention that our instantaneous assessment opens the possibility of analyzing the proposed measures also in terms of variability of their evolution along time, which we refer to as *complexity variability framework* [15, 18].

3. Experimental Protocol and Results

Bipolar ECG recordings (sampling frequency: 256 Hz) were collected from 10 patients (age: 40.4 ± 17 years) with at least one seizure originating from temporal regions as recorded by video-EEG monitoring. For each patient, we selected a) a 2-minute long artifact-free interictal period (INT) and b) a 2-minute long artifact-free period containing a seizure (CRI) occurring at rest and during wakefulness in supine state.

In 8 out of a total of 10 recordings of INT periods, and in 8 out of a total of 10 recordings of CRI periods, both KS plots and more than 98% of the autocorrelation samples fell within 95% confidence intervals.

KS distance analysis revealed a satisfactory goodness-of-fit, being as low as 0.0708 ± 0.0275 for recordings of CRI periods, and as low as 0.0537 ± 0.0187 for recordings of INT periods, with NARL orders of $p = 4$ and $q = 2$.

We summarized instantaneous estimates of mean RR interval $\mu_{RR}(t)$, RR standard deviation $\sigma_{RR}(t)$, heart rate standard deviation $\sigma_{HR}(t)$, spectral power within the low frequency (LF, 0.04-0.15 Hz), spectral power within the high frequency (HF, 0.15-0.40 Hz), the LF/HF ratio, and the instantaneous complexity ipApEn_m and ipSampEn_m, by computing median values over each recording period.

In addition, measures of complexity variability

$ipApEn_{mad}$ and $ipSampEn_{mad}$ were computed as median absolute deviation over each recording period.

All features were tested for significant effects (CRI vs. INT) using Wilcoxon non-parametric tests for paired data with null-hypothesis of equal medians.

Results are summarized in Table 1. Estimates of $ipApEn_m$ and $ipApEn_{mad}$ were significantly lower ($p < 0.03$) during CRI, as compared to INT. Estimates of $ipSampEn_m$ were also lower ($p < 0.065$). No other significant differences were detected.

Table 1: Instantaneous statistics from the CRI vs INT analysis, expressed as “median \pm median absolute deviation”

Index	CRI	INT	p-value
μ_{RR}	767.88 \pm 101.11	789.96 \pm 94.10	0.492
σ_{RR}	124.59 \pm 68.74	452.21 \pm 323.12	0.275
σ_{HR}	1.46 \pm 0.93	3.26 \pm 1.66	0.922
LF	106.31 \pm 87.89	341.89 \pm 320.77	0.160
HF	24.08 \pm 15.61	201.14 \pm 124.68	0.557
LF/HF	3.07 \pm 2.37	2.74 \pm 2.26	0.981
$ipApEn_m$	0.167\pm0.010	0.303\pm0.027	0.014
$ipApEn_{mad}$	0.019\pm0.003	0.023\pm0.002	0.027
$ipSampEn_m$	0.113\pm0.015	0.199\pm0.022	0.064
$ipSampE_{mad}$	0.018 \pm 0.009	0.031 \pm 0.006	0.232

Bold indicates statistically significant indices with $p < 0.065$. p-values are from the Wilcoxon non-parametric test for paired data with null-hypothesis of equal medians

Regarding instantaneous complexity measures, Figure 1 shows group-wise box-plot statistics, whereas Figure 2 shows exemplary estimates in time from one representative patient.

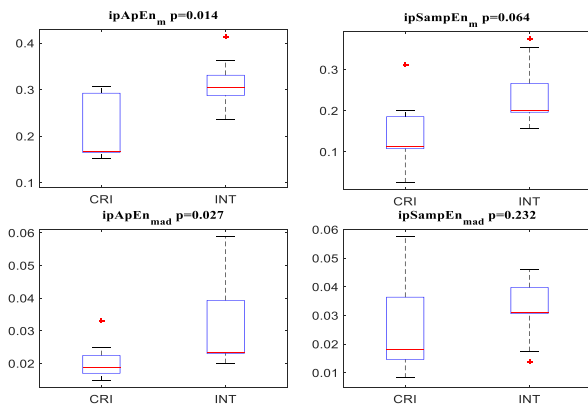


Figure 1: Box-plot statistics from instantaneous complexity analysis between CRI and INT.

4. Discussion and Conclusion

In this study, we demonstrate that ictal events in untreated TLE are associated with a significant decrease in heartbeat complexity over time, with respect to interictal periods. From a descriptive statistics point of view, such a decrease affects not only the central tendency, but also the variability of cardiovascular complexity computed over the recording periods. No other significant differences between CRI and INT samples were observed in features defined in the time and frequency domains. On a more general level, our results are in agreement with our previous findings showing that complex heartbeat dynamics is altered in mental disorders like major depression and bipolar disorders [17, 19]. Of note, a significantly altered instantaneous complex dynamics was also found to be associated to Parkinson’s disease [13]. A physiological justification of this result could be related to dysfunctions on the recruitment of the so-called Central Autonomic Network as well as other central circuits, which were recently linked to the spread of repetitive seizures discharges [9, 10].

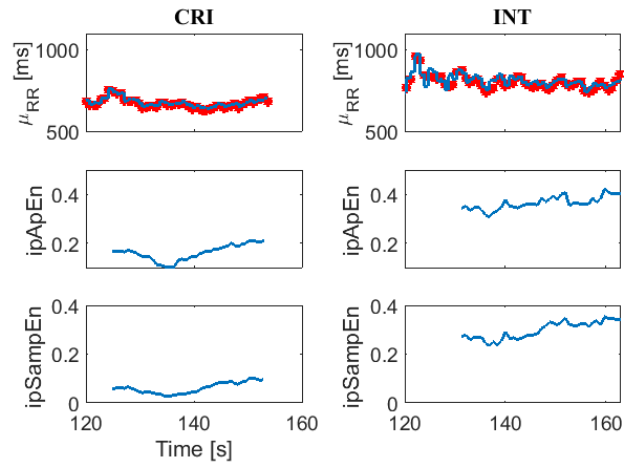


Figure 2: Instantaneous statistics from an exemplary patient.

From the top, the instantaneous mean (blue line) is superimposed to the RR interval series (red asterisks) during a CRI session (left column) and an INT observation (right column). Below, the instantaneous entropy measures are shown.

To our knowledge, the study of instantaneous complex cardiovascular dynamics is only possible by employing our recently defined point-process framework, allowing for the definition of inhomogeneous point-process approximate and sample entropy ($ipApEn$ and $ipSampEn$, respectively) [15]. As an important advantage, these measures are not affected by the statistical properties of the physiological noise behind the observed dynamics. This ensures that, when performing comparisons like the one presented in this study, lower values of $ipApEn$ and

ipSampEn are indeed associated with a lower instantaneous complexity as opposed to possible alterations in the noise statistics (e.g. a transition from 1/f noise to Gaussian noise).

In summary, our results point towards subtle autonomic changes which may accompany or precede seizures and can only be detected using an instantaneous, time resolved approach to quantifying autonomic complexity.

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