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Impairment of heart rhythm complexity in patients with drug-resistant epilepsy: An assessment with multiscale entropy analysis

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ABSTRACT

Objective: Epilepsy and seizures can have dramatic effects on the cardiac function. The aim of this study was to investigate the heart rhythm complexity in patients with drug-resistant epilepsy (DRE).
Methods: Ambulatory 24-h electrocardiograms (ECG) from 70 DRE patients and 50 healthy control subjects were analyzed using conventional heart rate variability (HRV) and multiscale entropy (MSE) methods The variation of complexity indices (CI), which was calculated from MSE profile, was determined.
Results: DRE patients had significantly lower time domain (Mean RR, SDNN, RMSSD, pNN50) and frequency domain (VLF, LF, HF, TP) HRV measurements than healthy controls. Of the MSE analysis, MSE profile, CI including Slope 5, Area 1–5, Area 6–15 and Area 6–20 were significantly lower than those in the healthy control group. In receiver operating characteristic (ROC) curve analysis, VLF had the greatest discriminatory power for the two groups. In both net reclassification improvement (NRI) model and integrated discrimination improvement (IDI) models, CI derived from MSE profiles significantly improved the discriminatory power of Mean RR, SDNN, RMSSD, pNN50, VLF, LF, HF and TP.
Significance: The heart rate complexity is impaired for DRE patients. CI are useful to discriminate DRE patients from subjects with normal cardiac complexity. These findings indicate that MSE method may serve as a complementary approach for characterizing and understanding abnormal heart rate dynamics in epilepsy. Furthermore, the CI may potentially be used as a biomarker in monitoring epilepsy.

1. Introduction

Epilepsy affects around 65 million people worldwide, and 30%–40% of these patients being refractory to medical treatment are considered as drug-resistant epilepsy (DRE) (Moshé et al., 2015; Kwan et al., 2010). Apart from high mortality and morbidity, epilepsy also leads to alterations of cardiac autonomic regulation, exhibited as an impairment of sympathetic and/or vagal modulation of cardiac activity (Lotufo et al., 2012; Jansen and Lagae, 2010; Sevcencu and Struijk, 2010).

Heart rate variability (HRV) analyses is a noninvasive, simple and effective method for assessing the functional state of the autonomic nervous system (ANS) and serves to predict potential risk to many cardiovascular diseases and neurological disorders (Lotufo et al., 2012; Jansen and Lagae, 2010). Indeed, reduced HRV and inhibited vagal modulation in epilepsy is associated with an increased risk of cardiac death, especially sudden unexpected death in epilepsy (SUDEP) (Jansen

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and Lagae, 2010; Sevcencu and Struijk, 2010; Gaitatzis et al., 2004; Jallon, 2004; Tomson et al., 2008;). However, conventional linear algorithms are often applied to calculate measures of HRV, even though the regulation of the ANS on cardiac activity is considered to be a nonlinear physiological activity (Costa et al., 2002; Costa et al., 2005; Manor et al., 2010). Therefore, efficient methods for characterizing the complex nonlinear dynamics of the heart remain to be established.

Since the normal heart rhythm is related to complex nonlinear dynamics, complexity of heart rate dynamics is postulated to represent consolidative capability of the ANS and other interacting control systems. These allow for responding to transient stressors for adaptation to the demands of an ever-changing environment (Costa et al., 2002; Costa et al., 2005). Though extensively used for the analysis of physiological time series, classical entropy-based complexity measures quantify only the regularity of time series on a single scale without straight-forward correspondence between regularity and complexity (Costa et al., 2002; Costa et al., 2005). However, diseased systems which actually present random heart rate dynamics may lead to obtaining paradoxically higher complexity through conventional single scale entropy methods. Recently, multiscale entropy (MSE) analysis has been introduced to measure the complexity of physiological data sets over different temporal scales, offering more differentiated and exact insights into the control mechanisms underlying nonlinear dynamics (Costa et al., 2002; Costa et al., 2005). At present, MSE has been extensively used to analyze several biological signals for diagnostics, classification, risk stratification, and prognosis of diseases such as stroke, heart failure, primary aldosteronism, patients undergoing peritoneal dialysis, Alzheimer's disease, autism spectrum disorder and Parkinson disease (Tang et al., 2015; Costa and Healey, 2003; Lin et al., 2015; Lin et al., 2016; Mizunoa et al., 2010; Catarino et al., 2011; Chung et al., 2013). Furthermore, several studies have applied MSE to EEG in patients with epilepsy to investigate the dynamical changes of EEG complexity (Ouyang et al., 2013; Lu et al., 2015; Zavalayoe et al., 2016). Previous studies have used approximate entropy (ApEn) and sample entropy (SampEn) to quantify heartbeat dynamics in patients with epilepsy (Ansakorpi et al., 2002; Ronkainen et al., 2005; Valenza et al., 2016), however, MSE analysis of heart rhythm dynamics in DRE patients have not yet been studied.

The present study aimed to investigate the complexity of ECG signals using MSE analysis in DRE patients. Furthermore, the complexity indices (CI) derived from the MSE profile were compared with conventional complexity measures and their association with clinical factors were explored.

2. Methods

2.1. Participants

DRE patients had undergone routine presurgical examination including imaging examination (MRI or PET), clinical history, neuropsychological testing, long term video-EEG and 24-h ECG recordings from seven hospitals (Beijing Tiantan Hospital Capital Medical University, Sanbo Brain Hospital Capital Medical University, TsingHua University YuQuan Hospital, Peking University First Hospital FengTai Hospital, Chinese PLA General Hospital, First Affiliated Hospital of PLA General Hospital and Navy General Hospital) between August 2014 and April 2016 were evaluated. Inclusion criteria were as follows: (1) age 5–60 years old; (2) having tried at least two appropriate AEDs tested to tolerance or to blood levels at upper end of the target range of which at least 2 have been tolerated at normal dose; (3) at least 1 seizure per month. Exclusion criteria were the following: (1) cardiopulmonary anomaly, progressive neurological diseases, asthma, mental disease, or any other known disease that might affect ANS function; (2) alcohol addiction, smoking, and sleep-related breathing disorders; (3) a history of medication or concomitant substances that may have impacted the autonomic function. Healthy control subjects were recruited into this study based on their medical history and physical examination results. The observed variables included their demographic data, seizure type, epilepsy duration, etiology, seizure frequency, number of antiepileptic drugs (AED) used, total dose of AED per day, presurgical MRI or PET findings, ictal scalp video-EEG characteristic and ECG recordings. This study was approved by the Institutional Review Committee of Beijing Tiantan Hospital Capital Medical University, and all subjects, or parents/guardians of subjects, gave informed consent in written form including for the collection of their information and usage for research. The methods in the study were carried out in accordance with the approved guidelines.

2.2. Ambulatory ECG recording and preprocessing

A 12-lead ambulatory ECG monitoring system (MIC-12H-3S, JincoMed, Beijing) with a digital sampling rate of 500 samples/second per channel was used to record consecutive 24-h ECG in all subjects. The conventional ambulatory ECG configurations of leads V5, which provided a stable and reliable signal was selected as the principal analysis lead. Participants underwent 24-h ECG monitoring in free running conditions and were asked to keep activity diaries to document time, duration and type of each daily physical activity and possible seizures during the recording period. All 24-h Holter recordings were performed automatically by a PC-based acquisition system (SkyHolter, JincoMed, Beijing). The annotated files were then carefully inspected and corrected manually by technicians for extracting the RR intervals from leads II and V5. The ECG episodes with possible seizures and the data recorded during periods within at least 50 min from seizure onsets were discarded to avoid their potential effects on MSE and HRV analyses. After preprocessing, only recordings with at least 22 h of data were included in the analyses. Then four-hour period of RR intervals in the day-time for awake state (between 9AM and 5PM) was selected from each recording (Lin et al., 2015; Lin et al., 2016). All ECG segments with a four-hour length were selected from the same period (daytime with sitting or lying in a quiet awake state) to reduce the variability of the circadian rhythm and physical activity. Only subjects with recordings of more than 80% of qualified normal sinus beats were included for further analyses (Lin et al., 2015; Lin et al., 2016).

2.3. Traditional HRV and MSE analyses

The mean RR interval values (Mean RR), the standard deviation of RR intervals (SDNN), the root mean square of successive differences between heartbeats (RMSSD), and the percentage of the absolute change in consecutive RR interval that exceeded 50 ms (pNN50) were calculated from the 24-h ECG recordings using recommended methods (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

Fast Fourier transform (FFT) was used to calculated the four main spectral components for the total power (TP) for the frequency range 0.0033–0.40 Hz; the very low frequency power (VLF) for the frequency range 0.0033–0.04 Hz; the low frequency power (LF) for the frequency range 0.04–0.15 Hz and the high frequency power (HF) for the frequency range 0.15–0.40 Hz and the ratio of LF to HF (LF/HF) (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

Entropy measures including ApEn, SampEn and MSE were also calculated based on four-hour ECG recordings (Pincus, 1991; Richman and Moorman, 2000). The MSE method comprised of two procedures: 1) Coarse-graining the signals into different time scales. E.g. for a given time series $\{x_i, \cdots, x_i, \cdots x_N\}$, multiple coarse-grained time series $y_j^{(\tau)}$ were constructed by averaging the data points within non-overlapping windows of increasing scale factor, τ. Each element of the coarse-grained time series was calculated according to the Eq. (1):