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RESEARCH ARTICLE

Deceleration and acceleration capacities of heart rate in patients with drug-resistant epilepsy

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Abstract

Objective Epilepsy and seizures can have dramatic effects on cardiac function. The aim of the present study was to investigate deceleration capacity, acceleration capacity and their 24-h fluctuations of heart rate variability in patients with drug-resistant epilepsy.

Methods Deceleration capacity, acceleration capacity of heart rate and their 24-h dynamics derived from the phase rectified signal averaging method as well as traditional measures were analyzed in 39 patients with drug-resistant epilepsy and 33 healthy control subjects using 24-h electrocardiogram recordings. The discriminatory power of heart rate variability measures were validated by assessment of the area under the receiver operating characteristic curve. Net reclassification improvement and integrated discrimination improvement models were also estimated.

Results Both deceleration capacity and absolute values of acceleration capacity were significantly lower in patients with drug-resistant epilepsy. The abnormal suppression of absolute deceleration capacity and acceleration capacity values were observed throughout the 24-h recording time (peaked at about 3 to 5 A.M.). Deceleration capacity had the greatest discriminatory power to differentiate the patients from the healthy controls. Moreover, in both net reclassification improvement and integrated discrimination improvement models, the combination of acceleration capacity or deceleration capacity with traditional heart rate variability measures has greater discriminatory power than any of the single heart rate variability features.

Interpretation Drug-resistant epilepsy was associated with a significant inhibition of vagal modulation of heart rate, which was more pronounced during the night than during the day. These findings indicate that phase rectified signal averaging method may serve as a complementary approach for characterizing and understanding the neuro-pathophysiology in epilepsy, and may provide a new clue to sudden unexpected death in epilepsy.

Keywords Deceleration capacity · Acceleration capacity · Drug-resistant epilepsy · Heart rate variability · Autonomic nervous system

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Introduction

More than 65 million people worldwide have epilepsy, which is a chronic non-communicable disorder of the brain that affects people of all ages. Between 30 and 40% of all epilepsy patients are refractory to medical treatment and considered to have drug-resistant epilepsy (DRE) [1, 2]. Epilepsy may not only lead to recurrent and unprovoked seizures, but also to alterations in cardiac autonomic regulation, exhibited as low vagal modulation associated with high sympathetic modulation of the heart rate, combined inhibition of sympathetic and vagal modulation of the heart rate, or inhibition of either the vagal or sympathetic modulation of the heart rate [3, 4]. In addition, sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in patients with DRE, with an estimated lifetime risk of 35% in this patient population [5]. Although the underlying mechanisms of SUDEP remain poorly understood, cardiac, respiratory and brainstem dysfunctions have been widely suggested as potential contributing factors [5, 6]. Furthermore, the authors of some studies have also concluded that most cases of SUDEP occur in or by the bed during the night, demonstrating that 24-h rhythms of cardiac, respiratory and brainstem activity may contribute to its pathogenesis [7, 8].

Heart rate variability (HRV) analysis is a non-invasive, simple and effective method for assessing the function of the autonomic nervous system (ANS) and is a common strategy used to predict the risk of many cardiovascular diseases and neurological disorders [9, 10]. However, conventional linear analyses are often applied to calculate measures of HRV, even though the regulation of cardiac activity by the ANS is considered to involve non-linear physiological mechanisms [11]. Although many studies have investigated the effects of epilepsy on the cardiac autonomic function using traditional linear HRV analyses, the results are still mixed or even contradictory [3, 4]. Despite the widespread application of HRV analysis, linear approaches are neither adequate nor appropriate to describe the non-linear properties of the HRV signal. Moreover, since traditional linear HRV analyses cannot accurately distinguish between the vagal and sympathetic activities of the ANS, interpretation of the HRV measures is more complex than generally appreciated, and there is potential for incorrect conclusions and for excessive or unfounded extrapolations [9, 12].

Therefore, efficient methods for characterizing the complex non-linear, non-stationary and quasi-periodic HRV signal remain to be established. In 2006, the phase rectified signal averaging (PRSA) method, which is a robust tool for the extraction of periodic and quasi-periodic oscillations masked by the noise and artifacts of complex signals, was introduced to quantify the coherence time for each quasi-periodicity and to separate processes occurring during increasing and decreasing parts of the signal [13, 14]. This method is based on the definition of anchor points in the signal that are used to align the oscillatory fluctuations, followed by an averaging of the surroundings of the anchor points [13]. The PRSA technique provides more differentiated insights into the non-linear dynamical characteristics of cardiac autonomic regulation and offers a novel approach by which to quantify the effects of the sympathetic and vagal nervous systems on cardiac physiology. Bauer et al. also found that deceleration capacity (DC) of the heart rate quantified by the PRSA method was a powerful predictor of mortality after myocardial infarction, better than that of the left ventricular ejection fraction, conventional measures of HRV and the combination of the two [14]. However, the controversial physiological interpretation of DC and acceleration capacity (AC) quantified by the PRSA method may considered as potential drawback.

The advantages of the PRSA method have been shown for the risk stratification and prognosis of cardiovascular diseases. However, to date there has been no assessment of deceleration-related and acceleration-related HRV based on the PRSA method in patients with DRE. In the study reported here, alterations in DC, AC and their 24-h fluctuations were evaluated with the aim to assess the efficacy of their values for assessing the cardiac autonomic function of patients with DRE. We postulate that DC and AC are, in terms of cardiac autonomic discrimination, better indices of cardiac autonomic function than the established global HRV indices.

Method

Participants

Patients affected by DRE as defined by the International League Against Epilepsy (ILAE) (adequate trials showing failure of two tolerated, appropriately chosen and used antiepileptic drug schedules) were examined [2]. All selected patients underwent complete pre-surgical evaluations, including long-term (interictal and ictal) video-electroencephalography, 24-h electrocardiogram (ECG) recordings, brain magnetic resonance imaging or positron emission tomography, as well as a comprehensive clinical and neuropsychological assessment as part of the diagnosis process to ascertain DRE. Inclusion criteria were: (1) age 18–60 years; (2) previous treatment with at least two appropriate antiepileptic drugs (AED) tested for tolerance or to blood levels at the upper end of the target range, of which at least two were tolerated at normal dose; (3) at least 1

seizure per month. Exclusion criteria: (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 autonomic function. Demographic data and clinical factors for each patient were collected, including included age, sex, body mass index, epilepsy duration, seizure frequency and number and daily dose of AED used by each patient. Healthy control subjects were recruited into this study based on their medical history and physical examination results. The exclusion criteria for the control subjects were a history of cardiovascular disease and mental disorders, such as coronary artery disease, atrial fibrillation, myocardial infarction, peripheral artery disease, heart failure, renal insufficiency, schizophrenia, depression, obsessive–compulsive disorder and anxiety. The Institutional Review Committee of Beijing Tiantan Hospital Capital Medical University approved this study, and all participants or their parents/guardians gave written informed consent for the collection of patient information and the use of this information for research. The methods in the study were carried out in accordance with the approved guidelines.

ECG recording and pre-processing

A 12-lead ambulatory ECG monitoring system (model MIC-12H-3S; JincoMed, Beijing, China) with a digital sampling rate of 500 samples/second per channel was used to record a consecutive 24-h ECG in all subjects. Participants underwent 24-h ECG monitoring in freely moving conditions and were asked to keep activity diaries, which included the time, duration and type of each daily activity and possible seizures during the whole recording period. We defined seven types of activity in accordance with those used by Warwick and colleagues in their study [15], namely, sleeping overnight; sitting quietly or lying quietly (includes reading, thinking, listening, watching TV, being a passenger in a vehicle); sitting busy (includes talking, eating, playing cards, typing, driving a vehicle, sewing, handcrafts, writing; light on-foot activities involving some walking and moving around or active work; moderate on-foot activities involving walking or moving around quite a lot and activities which involve some bursts of heavy work; strenuous activities including very heavy gardening and home activities; very strenuous activities such as rowing, cycling, squash, running, among others. The amount of time patients and healthy controls spent doing the different types of activity that determined their activity level were analyzed.

HRV was analyzed based on the 24-h ambulatory ECG recordings. The ECG episodes with possible seizures and the data recorded during periods within at least 50 min of seizure onset were discarded to avoid their potential effects on DC, AC and HRV measurements [16]. The QRS wave complex of the recorded ECG signal was first classified automatically with a PC-based acquisition system (Sky-Holter; JincoMed) and then checked manually and adjusted by technicians. Since patients with epilepsy have wide variations in HRV [17], the heartbeat intervals (RR time series) were obtained without filtering. At least 21 h of a 24-h ECG recording had to be suitable for a record to be included in the analysis of circadian rhythm [18].

DC and AC calculations

To quantify the DC and AC for all participants, we applied the phase rectified signal averaging (PRSA) technique to process the heartbeat interval time series obtained from the 24-h ambulatory ECG recordings. The DC and AC were computed according to Bauer et al. [13, 14] as follows: (1) accelerating and decelerating anchor points are determined on the time series of the heartbeat interval; (2) segments of the heartbeat interval time series centered on each anchor point are selected; (3) all of the above segments are finally aligned and averaged; (4) the PRSA signal, *PRSA(I)*, is obtained by averaging the signals within the aligned segments; (5) the DC and AC are calculated based on Eq. (1), with a segment length (L) = 32, timescale (T) = 1 and wavelet scale (s) = 2. In the final analysis of 24-h rhythms of DC and AC, each heartbeat interval time series was divided into segments with a length of 3600 s. The short-term DC and AC were calculated from each heartbeat interval segment for further 24-h rhythm analysis.

$$\mathrm{DC(or\ AC)} = \frac{1}{2s}\sum_{i=1}^{s}\mathrm{PRSA}(L+I) - \frac{1}{2s}\sum_{i=0}^{s-1}\mathrm{PRSA}(L-I). \quad (1)$$

Traditional linear HRV analysis

The resting heart rate was measured from a 5-min ECG segment, which was selected from the same period (between 8 p.m. and 9 p.m., with subjects lying quietly in an awake state) to reduce the variability and influence of the circadian rhythm and physical activity. The time domain and frequency domain HRV measures were calculated from the 24-h ECG recordings using recommended methods [9]. The mean RR intervals (Mean RR), standard deviation of the RR intervals (SDNN), square root of the mean of the sum of the squares of the differences between adjacent RR intervals (RMSSD), and percentage of the absolute change in consecutive normal RR intervals that exceeds 50 ms (pNN50) were obtained with a simple way. SDNN reflects a global measure of HRV while RMSSD provides a useful evaluation of vagal modulation of the heart rate [10]. However, these measures do not

provide the means to adequately quantify cardiac autonomic function or determine the rhythmic activity generated by the different physiological control mechanisms related to the heart. A fast Fourier transform was used to calculate the four main spectral components, namely, total power (TP; 0.0033–0.40 Hz), very low frequency (VLF; 0.0033–0.04 Hz), low frequency (LF; 0.04–0.15 Hz) and high frequency (HF; 0.15–0.40 Hz) [9]. It has been suggested that LF reflects the modulations of both the parasympathetic and sympathetic nervous systems, whereas HF primarily reflects parasympathetic nervous system activity. Recent experimental results suggests that the VLF spectral component appears to be generated intrinsically by the heart itself and that the frequency and amplitude of these oscillations are regulated by efferent sympathetic activity [9, 10].

Statistical analysis

Gaussian distribution and tests for homogeneity of variance were applied to determine the distribution and homoscedasticity of DC, AC and the traditional HRV measures. Because of the non-normal distribution and heterogeneity of variance of some measures, data were presented as the median with the interquartile range for continuous variables. Mann–Whitney *U* tests were applied to examine the differences in variables between the patients with DRE and the healthy control subjects. For the single predictive variable analysis using qualitative or categorical variables, we used Fisher's exact tests to compare the two groups. The single cosinor method was used to analyze hourly mean values of DC and AC [19]. Three parameters, including MESOR, amplitude and acrophase, were characterized to illustrate the characteristic of a cardiovascular daily rhythm. The significance of the 24-h rhythms was evaluated by the zero amplitude test. The relationship between the HRV indices and the demographic/clinical factors was analyzed using multiple regression analysis. To compare the ability of DC, AC and traditional HRV indices to differentiate the DRE patients from the healthy control subjects, we used receiver operating characteristic (ROC) curve analysis and calculated the area under the ROC curve (AUC). C-statistics was used to describe the discrimination of the models before and after adding the confidence interval [20–22]. The net reclassification improvement (NRI) and integrated discrimination improvement (IDI) models were used to assess improvements in prediction using two different logistic regression models, with 0.2 and 0.4 used as the cutoff points [21, 22]. All statistical analyses were performed using SPSS version 20 (IBM Corp., Armonk, NY, USA) and Matlab R2013 (MathWorks Inc., Natick, MA, USA). All the p values were adjusted using the false discovery rate method, and a value of $p < 0.05$ was considered to indicate statistical significance.

Results

Study population

A total of 39 patients with DRE and 33 healthy control subjects met the inclusion criteria and were included in the study. Among the 39 DRE patients, five reported having experienced possible seizures during the 24-h ECG recording, and 11 patients reported having focal seizures, with each seizure attack not exceeding 60 s. As the HRV of the five patients reporting a possible seizure during the ECG recording was not particularly different from that of the other patients, we considered that that the occurrence of seizures did not significantly affect our results. Demographic data and clinical factors of patients with DRE are presented in Table 1and Electronic Supplementary Material (Table E). There were no significant differences between patients and controls in terms of demographic data and clinical factors. In addition, there was no statistically significant difference between the patients with DRE and the healthy control subjects on the different types of daily physical activity. Detailed information on the clinical and therapeutic characteristics of the 39 patients with DRE is given in Table 2.

DC, AC and traditional HRV parameters

The results of the PRSA, time domain analysis and frequency domain analysis of HRV from 24-h ECG recordings in patients with DRE and healthy controls are shown in Table 3. With regard to the PRSA indices, Both DC ($p < 0.001$) and absolute values of AC ($p < 0.001$) were significantly lower in the DRE group than in the healthy control group. All of the analyzed traditional linear HRV measurements were significantly lower in the DRE patients (all $p < 0.001$) than in healthy control subjects, with the exception of the LF/HF ($p = 0.692$) and resting heart rate ($p = 0.668$). In the multiple regression analyses, SDNN positively correlated with the seizure frequency of patients with DRE ($\beta = 0.519$, $p < 0.001$) , while SDNN ($\beta = -0.555$, $p = 0.002$), RMSSD ($\beta = -0.475$, $p = 0.029$), VLF ($\beta = -0.554$, $p = 0.011$), LF ($\beta = -0.480$, $p = 0.029$) and TP ($\beta = -0.523$, $p = 0.018$) negatively correlated with the total daily dose of AED. Moreover, there were no independent factors associated with AC and DC in the final models.

Table 1 Demographic data, clinical factors, physical activity types and epilepsy duration for patients with drug-resistant epilepsy and healthy control subjects

Demographic data and clinical factors	Healthy control subjects (n = 33)	Patients with DRE (n = 39)	p value
Male/female	25/8	28/11	0.792
Age (years)	25 (23–28)	25 (19–30)	0.727
Body mass index (kg/m^2)	22.34 (21.28–23.54)	23.39 (20.83–27.04)	0.064
Epilepsy duration (years)	N.A.	13 (10–17)	N.A.
Seizures per month	N.A.	13 (6–60)	N.A.
Number of AEDs	N.A.	2 (1–3)	N.A.
Total dose of AEDs per day (mg)	N.A.	1500 (1000–2350)	N.A.
Physical activity			
Sleeping overnight (h)	8.0 (8.0–9.0)	8.0 (7.0–9.0)	0.669
Sitting quietly or lying quietly (h)	3.4 (2.7–3.9)	3.0 (2.3–4.9)	0.938
Sitting busy (h)	5.4 (5.4–6.0)	5.0 (4.0–6.1)	0.599
Light on-foot activities (h)	5.1 (4.5–6.2)	5.0 (3.1–6.6)	0.510
Moderate on-foot activities (h)	2.0 (1.0–2.7)	2.0 (1.1–2.5)	0.585
Strenuous activities (h)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	1.000
Very strenuous activities (h)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	1.000

Values are presented as number or as the median with the interquartile range (IQR) in parenthesis

DRE drug-resistant epilepsy,*AED* anti-epileptic drugs, *N.A.* not available

Table 2 Clinical and therapeutic data for the 39 patients with drug-resistant epilepsy

Characteristics	Number of patients in each sub-category
AED therapy	Single drug: 11; multiple drugs:28
Type of AED	VPA: 21; LTG: 12; CBZ: 17; OXCBZ: 7 LEV: 8; TPM: 5; PHB: 6; CZP: 3 PHT: 4; MGVPA: 4; CPNCM: 2; DZP: 2 TCM: 2; GBP: 1
Seizure type	GS: 12; FS: 3; GS + FS: 24
Seizure frequency per month	≤ 10: 18; > 10: 21
Ictal scalp EEG characteristics	Single focus: 3; multifocal: 25; unknown: 11
Etiology	Cryptogenic: 24; symptomatic: 15

EEG Electroencephalography, *VPA* valproate, *LTG* lamotrigine, *CBZ* carbamazepine, *OXCBZ* oxcarbazepine, *LEV* levetiracetam, *TPM* topiramate, *PHB* phenobarbital, *CZP* clonazepam, *PHT* phenytoin, *MGVPA* magnesium valproate, *CPNCM* compound phenobarbital nitrazepam and chlorphenamine maleate, *DZP* diazepam, *TCM* traditional Chinese medicine, *GBP* gabapentin, *GS* generalized seizure, *FS* focal seizure

24-h rhythms of the DC and AC

The hourly mean DC and AC of both the patients with DRE and the healthy controls showed significant circadian rhythms (Fig. 1). DC and absolute values of the AC increased at night and decreased during the day. The parameters characterizing the circadian rhythms of DC and AC are summarized in Table 4. The MESOR, amplitude and acrophase of DC were similar in the patients with DRE and the healthy controls, as were those of AC. In addition, both the DC and absolute values of AC for the patients with DRE were suppressed throughout the 24-h recording time (Fig. 1). The differences in DC and AC between the patients with DRE and healthy control subjects were more pronounced during the night, approximately peaking between 3 a.m. and 5 a.m.

ROC curve analysis

In the ROC curve analysis, DC (AUC = 0.818) had the greatest discriminatory power for the DRE patients and healthy control subjects compared to AC and the other traditional HRV parameters (Fig. 2). The AUC of Mean RR, SDNN, RMSSD, pNN50, VLF, LF, HF, TP, AC and DC were 0.660, 0.743, 0.735, 0.719, 0.796, 0.776, 0.693, 0.759, 0.810 and 0.818, respectively. In both the NRI and IDI models, the combination of AC or DC with traditional HRV measures had the greater discriminatory power than any of the HRV features singly (Table 5).

Table 3 Time domain, frequency domain heart rate variability parameters and deceleration and acceleration capacity, respectively, in the patients with drug-resistant epilepsy and the healthy control subjects

Variables	Healthy control subjects (n = 33)	Patients with DRE (n = 39)	p value
Resting heart rate (bpm)	80 (75–90)	79 (76– 89)	0.668
Mean RR (ms)	797(776–842)	753 (696–821)	0.020
SDNN (ms)	165 (138–187)	124 (98–159)	< 0.001
RMSSD (ms)	40 (33–51)	30 (21–40)	< 0.001
pNN50 (%)	17.21 (10.37–21.40)	10.08 (2.93–16.60)	0.001
VLF (ms^2)	203 (156–282)	125 (81–176)	< 0.001
LF (ms^2)	986 (733–1662)	629 (316–778)	< 0.001
HF (ms^2)	643 (361–1194)	382 (180–684)	0.005
TP (ms^2)	1753 (1304–3136)	1087 (605–1630)	< 0.001
LF/HF	1.66 (1.10–2.18)	1.43 (1.13–2.11)	0.692
AC (ms)	− 15.64 (− 17.90 to − 13.99)	− 9.79 (− 14.52 to − 8.15)	< 0.001
DC (ms)	15.10 (13.06–18.29)	10.53 (8.18–13.84)	< 0.001

Values are presented as the median with the IQR in parenthesis

Mean RR Mean RR interval, *SDNN* standard deviation of the RR intervals, *RMSSD* square root of the mean of the sum of the squares of the differences between adjacent RR intervals, *pNN50* percentage of the absolute change in consecutive normal RR interval that exceeds 50 ms, *VLF* very low frequency, *LF* low frequency, *HF* high frequency, *TP* total power, AC acceleration capacity, *DC* deceleration capacity

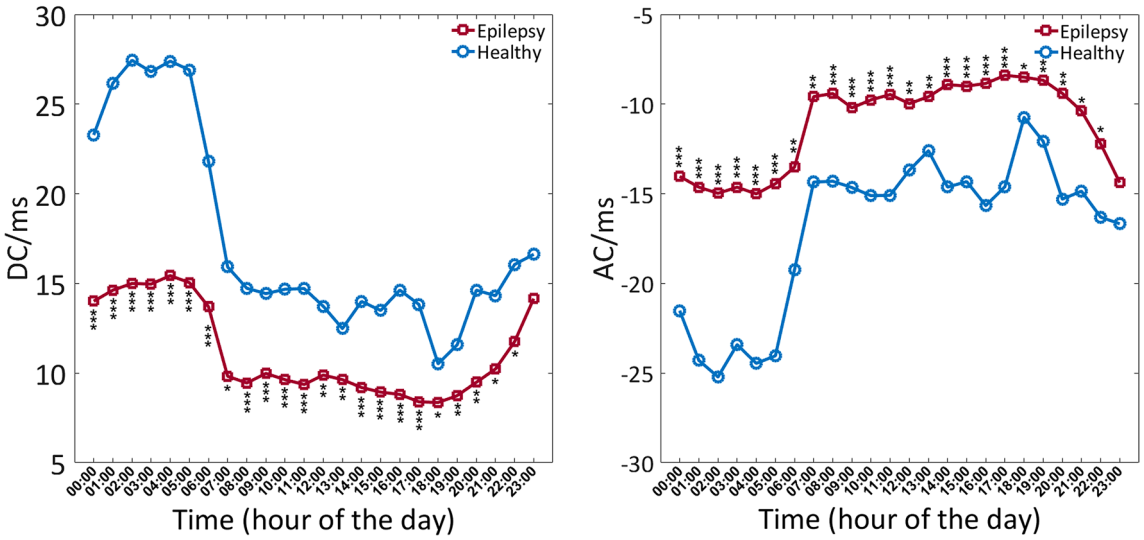

Fig. 1 Median 24-h fluctuations in deceleration capacity (*DC*) and acceleration capacity (*AC*) inthe heart rate of patients with drug-resistant epilepsy (DRE) and their healthy matched controls. Asterisks indicate significant differences between patients and controls at $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ using the Mann–Whitney *U* test

Table 4 Chronobiological parameters of 24-h deceleration capacity and acceleration capacity rhythms for the patients with drug-resistant epilepsy and the 33 healthy controls

Variables	MESOR	Amplitude	Acrophase	p value
DRE patients				
DC	261.50	253.09	− 3.40	< 0.001
AC	− 265.50	257.32	− 0.24	< 0.001
Healthy controls				
DC	268.39	256.10	− 3.44	< 0.001
AC	− 275.79	263.23	− 0.29	< 0.001

Discussion

To the best of our knowledge, this is the first study to use the novel PRSA technique to investigate DC, AC and their circadian rhythms in patients with DRE. The major findings of our study are: (1) DRE was associated with suppressed magnitude of DC, AC and traditional HRV measures; (2) the circadian rhythms of DC and AC did not differ significantly in the two groups, while suppressed DC and absolute AC values were observed in DRE patients throughout the

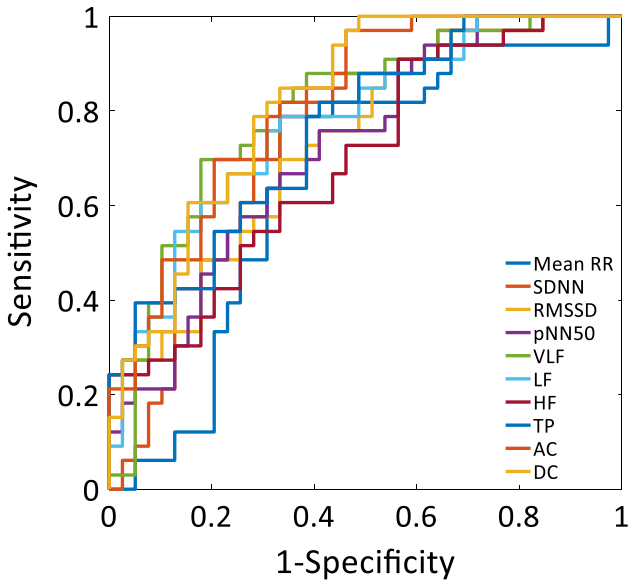

Fig. 2 Analysis of the discrimination power of the two groups by receiver operating characteristic curve analysis. The areas under the curve of Mean RR, SDNN, RMSSD, pNN50, VLF, LF, HF, TP, AC and DC were 0.660, 0.743, 0.735, 0.719, 0.796, 0.776, 0.693, 0.759, 0.810 and 0.818, respectively. See footnote to Table 3 for definition of abbreviations

24-h EEG recording time with the between-group difference peaking approximately between 3 a.m. and 5 a.m.; (3) DC was the best factor to classify DRE, with an AUC of 0.818, and the combination of AC or DC with traditional HRV measures had greater discriminatory power than any of the HRV features singly.

ANS balance plays a vital and sophisticated role in maintaining the homeostasis of normal physiological processes in the human body [10, 23]. HRV measurements provide information on the degree of regulation of the heart rate, and these are often used as indirect indices to evaluate cardiac autonomic function. With respect to the spectral components of HRV, LF reflects the modulations of both the sympathetic and the parasympathetic nervous system, whereas HF mainly reflects parasympathetic nervous system activity [10]. The LF/HF ratio is an assessment of the global balance between sympathetic and parasympathetic nervous system activity [24]. However, traditional methods of analyzing HRV do not distinguish clearly between the vagal and sympathetic modulation of heart rate. Consequently, the PRSA method for quantifying DC and AC, two parameters which reflect cardiac vagal modulation of the heart rate, was introduced, and this method now is used as a prognostic tool for risk stratification in cardiovascular diseases and neurological

Table 5 Area under the curve, net reclassification improvement and integrated discrimination improvement models of traditional linear heart rate variability measurements before and after the addition of acceleration capacity and deceleration capacity to the model

Parameters	AUC	R^2	NRI	NRI *p* value	IDI	IDI *p* value
Mean RR	0.660	0.063				
AC	0.820	0.404	0.429	0.003	0.256	<0.001
DC	0.836	0.430	0.497	0.001	0.282	<0.001
SDNN	0.743	0.218				
AC	0.819	0.419	0.491	0.001	0.082	0.001
DC	0.834	0.440	0.600	<0.001	0.095	<0.001
RMSSD	0.735	0.242				
AC	0.814	0.402	0.429	0.003	0.128	0.003
DC	0.825	0.422	0.389	0.008	0.147	0.001
pNN50	0.719	0.186				
AC	0.814	0.401	0.360	0.013	0.164	0.001
DC	0.826	0.425	0.497	0.001	0.186	<0.001
VLF	0.796	0.244				
AC	0.832	0.422	0.291	0.045	0.126	0.005
DC	0.841	0.444	0.211	0.146	0.143	0.002
LF	0.776	0.269				
AC	0.824	0.416	0.103	0.480	0.112	0.007
DC	0.834	0.443	0.240	0.099	0.133	0.002
HF	0.693	0.197				
AC	0.814	0.401	0.417	0.004	0.164	<0.001
DC	0.820	0.422	0.423	0.004	0.183	<0.001
TP	0.759	0.277				
AC	0.816	0.409	0.171	0.239	0.106	0.007
DC	0.826	0.431	0.200	0.169	0.125	0.002

AUC Area under the receiver operating characteristic curve, *NRI* net reclassification improvement method, *IDI* integrated discrimination improvement method

disorders, such that it has been demonstrated that a lower DC is significantly related to a higher risk of death [12, 14, 25–30].

Epilepsy and recurrent seizures can have profound effects on interictal and ictal cardiac autonomic function [3]. It has been previously documented that decreased HRV and autonomic dysregulation may induce lethal arrhythmias in patients with epilepsy [31]. Time domain, frequency domain and non-linear HRV analyses have also been applied to investigate the cardiac autonomic function of patients with epilepsy (especially those with temporal lobe epilepsy), but the findings to date have been mixed or even contradictory [32–40]. The results of our study show that our patients with DRE had lower Mean RR, SDNN, RMSSD, pNN50, TP, VLF, LF and HF than did their healthy controls, thereby confirming that DRE patients have an impaired cardiac autonomic regulation with a significantly overall reduced HRV. Taken together, these data suggest an impairment of the ANS affecting both the vagal and the sympathetic branches. Furthermore, the lower RMSSD, pNN50 and HF are definitely the result of a reduction of vagal modulation of the heart rate, but the cardiac sympathetic regulation is difficult to determine based on HRV parameters. Several research groups have reported significantly altered HRV measurements in patients with epilepsy compared to healthy controls [32–41]; however, the duration of ECG recordings, HRV analysis methods, variables, characteristics and sample size of patients used as well as study protocols are very diverse in different studies, and thus the results of each study are difficult to compare totally.

To date, there have been no reports of DC, AC and their 24-h rhythms in epilepsy. Bauer et al. reported that DC and AC could provide non-invasive assessments of cardiac vagal and sympathetic modulations, respectively [14]. Up to the present this method has been applied primarily in risk stratification of cardiovascular disease, but not yet in the assessment of cardiac autonomic function in patients with DRE. In our study, we observed significant lower DC and absolute AC values in our patients with DRE, which reflected a loss of vagal modulation of heart rate in these patients. More importantly, DC and AC significantly improved the discriminatory power of traditional HRV measurements. Our results indicate the additive effects of traditional HRV parameters and DC (or AC) to differentiate DRE patients from healthy controls with normal cardiac autonomic function. Our observation of the withdrawal of vagal modulation is in line with the findings of previous studies based on traditional HRV analyses [39, 40]. AC characterizes the capacity to speed the heart up, which illustrates the total acceleration capacity of the sinus rhythm, unnecessarily being combined with one special physiological adjustment process. According to a recent study by Pan et al., both DC and AC are solely dependent on vagal activity under conventional conditions ($T = 1, s = 2$) [42]. Therefore, our observation of a decrease in the magnitude of AC, which also reflects a depression of parasympathetic nervous system in DRE patients, is consistent with previously reported evidence [32–38]. In fact, ictal tachycardia is commonly observed in the clinic for patients with DRE [3]. We also found that the interictal Mean RR of DRE patients was significantly shorter than that in healthy control subjects, which may possibly be an indication of sympathetic activation.

Impaired cardiorespiratory regulatory functions in epilepsy may be involved in the pathogenesis of SUDEP, which is the most common cause of death in patients with epilepsy [5, 43]. Previous studies have reported that SUDEP occurs most often at night or during sleep [7–9]. There is evidence of suppressed circadian HRV in epileptic patients [32, 36–38, 40, 43, 44], and it is important to note that most studies have selected patients with temporal lobe epilepsy as their subjects and that these results cannot be extrapolated to people with epilepsy in general. In the present study, both DC and AC of the two groups showed significant circadian rhythms. However, the patients with DRE were found to have a significantly lower magnitude of DC and AC than did the healthy controls, with a more significant nocturnal difference (peaking at about 3–5 a.m.), indicating a inhibited vagal modulation of the heart rate throughout the 24-h monitoring time. Persson et al. [44] previously found a decrease in HRV in patients with epilepsy that more pronounced during the night, thus affecting the circadian HRV. Ronkainen et al. [38] reported the depression of the circadian rhythms of the HF and LF spectral components in patients with temporal lobe epilepsy. These authors also found that the HF spectral component of epileptic patients was significantly lower than that in healthy controls between 11:00 p.m. and 10:00 a.m., thereby demonstrating that there was no significant difference in vagal modulation of the heart rate in both the epileptic patients and healthy control subjects during the daytime [38]. These observations based on traditional HRV indices are inconsistent with our findings. Such differences may be due to the homogeneity of their cohort [38], which comprised only patients with epilepsy occurring in specific brain regions in order to provide a consequential comparison to healthy controls. In our study, we evaluated circadian rhythm of cardiac autonomic function with only ECG signals. As previously described, variation of sleep determined by EEG is associated with diurnal fluctuation in HRV [17, 45]. Without validated subjective scales or clinical evaluation, it is difficult to exclude the influences of sleep- or sleep stage-specific circadian modulation of the autonomic control of the heart in the light of the high prevalence of sleep events in patients with epilepsy [46]. Future polysomnographic studies are warranted to help clarify the interaction between sleep phases

and the circadian rhythm of HRV in epileptic patients. The PRSA method used in our study has a number of significant advantages over traditional methods in terms of analyzing the non-linear, non-stationary and quasi-periodic ECG signal. The potential relevance of our observations on the more pronounced suppression of vagal modulation of the heart rate during the night (especially between approx. 3 a.m. and 5 a.m.) for the risk of SUDEP remains to be elucidated, but these findings provide a new clue to the cause of SUDEP. Our results suggest that the PRSA method may be applied in future studies for risk stratification, prognosis and treatment assessment in DRE patients.

Our study has a number of limitations. First, it included patients receiving various AED, whereby the effects of these different AED on the cardiac autonomic function may be unpredictable. It is also difficult to distinguish a specific effect caused by a certain AED. Second, we recruited heterogeneous DRE characterized by different types of seizures and various localizations/lateralizations of epileptic focus; the potential effects of these differences should be elucidated in future studies. Third, our findings are based on a small sample size of patients with DRE and thus we were unable to discriminate between other possible contributing factors.

Conclusion

Drug-resistant is associated with diminished HRV and with diminished magnitude of DC and AC, thereby reflecting the loss of vagal modulation of the heart rate. This abnormal change in cardiac autonomic function in patients with DRE is more pronounced during the night than during the day. We found that DC was the best HRV index to classify DRE and that the combination of AC or DC with traditional HRV measures had a greater discriminatory power than any one of the HRV features used alone. Our findings suggest that DC and AC are more accurate parameters than other HRV measures to assess cardiac autonomic function in patients with DRE. This newly introduced quantification of HRV may provide new insights into the cardiac health of patients with DRE.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval The study protocol was approved by the Institutional Review Committee of Beijing Tiantan Hospital Capital Medical University (No. qx2014-010-02), and all subjects (or parents/guardians of subjects) provided written informed consent.

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