Pre-ictal heart rate variability assessment of epileptic seizures by means of linear and non-linear analyses

Doğrusal ve doğrusal olmayan analiz yoluyla epileptik nöbetlerin (iktal) kriz öncesi kalp hızı değişkenliği ile değerlendirilmesi

Soroor Behbahani, Nader Jafarnia Dabanloo, Ali Motie Nasrabadi[1], Cesar A. Teixeira[2], Antonio Dourado[2]

Department of Biomedical Engineering, Science and Research Branch, Islamic Azad University, Tehran-*Iran*
[1]Department of Biomedical Engineering, Shahed University, Tehran-*Iran*
[2]Center of Informatics and Systems (CISUC), University of Coimbra, Coimbra-*Portugal*

ABSTRACT

Objective: The purpose of the present study was to analyze the effects of epilepsy on the autonomic control of the heart in pre-ictal phase in order to find an algorithm of early detection of seizure onset.
Methods: Overall 133 epileptic seizures were analyzed from 12 patients with epilepsy (seven males and five females; mean age 43.91 years, SD: 10.16) participated in this study. Single lead electrocardiogram recordings of epileptic patients were compiled. 240, 90-30, 30-10 and 5 minutes heart rate variability (HRV) signals of preseizure were chosen for analysis of heart rate. As HRV signals are non-stationary, a set of time and frequency domain features (Mean HR, Triangular Index, LF, HF, LF/HF) and nonlinear parameters (SD1, SD2 and SD2/SD1 indices derived from Poincaré plots) extracted from HRV is analyzed. Statistical analysis was performed using paired sample t-test for comparisons of the segments and differences between pre-ictal segments were evaluated by Tukey tests.
Results: There was slight tachycardia in segments near the seizure (30 minutes before: 85.3517 bpm, 5 minutes before: 119.3630.82 bpm, p=0.0207) which significantly differ from baseline in segments far from seizure (240 minutes before: 66.5211.7 bpm). Also there was significant increase in LF/HF ratio (30 minutes before: 1.10.22, 5 minutes before: 2.120.5, p=0.0332) and SD2/SD1 ratio (30 minutes before: 1.20.15, 5 minutes before: 2.030.55, p=0.0431) when compared to segments far from the seizure (240 minutes before: 0.780.24 and 0.780.14) respectively. Although there was about decrease of triangular index in segments near the seizure the percentage of decrease was not comparable to segments far from the seizure.
Conclusion: Significant changes of HRV parameters in pre-ictal (5 minutes before the seizure) are obviously higher in comparison to interictal baseline. Pre-ictal significant changes of HRV suggesting that this time can be considered as prediction time for designing an algorithm of early detection of seizure onset based on HRV. *(Anadolu Kardiyol Derg 2013; 13: 797-803)*
Key words: Heart rate variability, epileptic seizure, pre-ictal, detection

ÖZET

Amaç: Bu çalışmanın amacı epilepsinin kriz öncesi preiktal döneminde kalbin otonomik kontrolü üzerine etkilerinin nöbet başlangıcının erken teşhisi algoritmasını bulmak adına incelenmesiydi.
Yöntemler: Bu çalışmaya katılan 12 epilepsi hastasının 133 epilepsi nöbeti analiz edildi. (yedi erkek ve beş kadın; ortalama yaş 43,91, SD:10,16). Epileptik hastaların tek kanal EKG kayıtları derlendi. Kalp atış hızı analizi için 240, 90-30, 30-10 ve 5 dakikalık nöbet öncesi HRV sinyalleri seçildi. HRV sinyalleri durağan değilken, zaman dilimleri ve frekans alanı özellikleri (HR ortalaması, üçgen indeks, LF, HF, LF/HF), HRV'den elde edilen doğrusal olmayan değişkenler (Poincaré grafiklerinden elde edilen SD1, SD2, ve SD2/SD1 indeksleri) analiz edildi. İstatiksel analiz, segmentlerin karşılaştırılması için Wilcoxon kullanılarak gerçekleştirildi ve kriz öncesi segmentlerin arasındaki fark Tukey testi ile değerlendirildi.
Bulgular: Nöbete yakın segmentlerde, uzak olan segmentlerdeki alt sınırdan (240 dakika önce: 73,5211,7 bpm) önemli ölçüde farklı hafif taşikardi vardı (10 dakika önce: 96,1722,55 bpm, 5 dakika önce 119,3630,82 bpm, p=0,0207). Ayrıca nöbetten uzak alan kesimlerle (sırasıyla 240 dakika önce: 0,790,24 and 0,830,11) karşılaştırıldığında LF/HF oranında (10 dakika önce: 1,280,4, 5 dakika önce: 1,740,77, p=0,0386) ve SD2/SD1 oranında (10 dakika önce: 1,080,26, 5 dakika önce: 1,30,15, p=0,0481) önemli bir artış vardı. Nöbete yakın segmentlerde üçgen indekslerde düşüş olmasına rağmen düşüşün yüzdesi uzak olan segmentlerle kıyaslanabilir değildi.
Sonuç: Kriz öncesinde (nöbet öncesi 5 dakika) HRV parametrelerinin değişimi kriz esnasındaki alt sınıra göre açıkça daha yüksektir. HRV'deki önemli kriz öncesi değişimler gösteriyor ki bu süre HRV'ye dayalı nöbet başlangıcı erken teşhisi algoritması tasarımı için tahmini süre olarak düşünülebilir. *(Anadolu Kardiyol Derg 2013; 13: 797-803)*
Anahtar kelimeler: Kalp hızı değişkenliği, epileptik nöbet, kriz öncesi, algılama

Address for Correspondence/Yazışma Adresi: Soroor Behbahani, Department of Biomedical Engineering, Science and Research Branch, Islamic Azad University, Tehran-*Iran* Phone: 00982177874289 E-mail: sor.behbahani@gmail.com
Accepted Date/Kabul Tarihi: 06.03.2013 **Available Online Date/Çevrimiçi Yayın Tarihi:** 07.10.2013

doi:10.5152/akd.2013.237

Introduction

In humans, epilepsy is the second most common neurological disorder, next to stroke, affecting 50 million people worldwide. Of these individuals, 25% do not respond to available therapies (1). Despite 40 years of research into the physiology of epilepsy, it is still not possible to explain how and when spontaneous clinical seizures emerge from the relatively normal brain state observed between them (2-9). An early in time prediction of epileptic seizures would considerably increase the quality of life in patients who cannot be successfully treated by common therapeutic strategies.

Dysfunction of the autonomous nervous system (ANS) has been reported in humans with epileptic seizures and in animal models (10-16). This dysfunction results in higher morbidity and mortality in patients with epilepsy than in those without epilepsy (17). Frequency-domain analysis of heart rate variability (HRV) is a sophisticated and noninvasive tool for detecting autonomic regulation of the heart (11, 14, 18-24).

Most studies have shown changes in cardiac autonomic parameters which occur in more than 90% of patients with complex partial and generalized tonic-clonic seizures. Autonomic dysfunction has also been noted in the interictal period, could be the only sign during this phase of clinical calm, and might play an important role in the cause of Sudden unexpected death in epilepsy (SUDEP) (25, 26).

HRV before, during and after the seizure can be an indicator of the effect of sympathetic and parasympathetic input to the heart (24). Changes in HRV vary between seizure types; for example in temporal lobe seizures, increased sympathetic and decreased vagal heart rate modulation often precedes ictal electroencephalographic (EEG) changes (27-29). Previous studies have reported diminished interictal HRV in temporal lobe epileptic patients using conventional short and long- term electrocardiogram (ECG) recordings, but general study with focused on changes in heart rate during pre-ictal phase failed, and many aspects of it has remained unclear (25, 30-33).

HRV can give valuable information when used as an adjunct during clinical seizures. As using time and frequency domain parameters of HRV are not always suitable for analysis because of the non-stationary characteristic of the ECG, some of non-linear methods such as the Poincaré plot are being increasingly used because they can be computed from shorter ECG records (34-37).

In this study, we used time-frequency domain and non-linear analysis to assess HRV changes during sympathetic and parasympathetic regulation in pre-ictal phase of epileptic seizures. The long-term goal of the study is to develop an algorithm based on ECG analysis that is able to detect and anticipate epileptic seizures with high sensitivity and specificity.

Methods

Study design

This study enrolled patients with pharmaco-resistant focal epilepsies who underwent pre-surgical evaluation. Recordings were obtained at the epilepsy units of the University Hospital of Freiburg, Germany; the Pitié-Salpêtrière Hospital of Paris, France; and the University Hospital of Coimbra, Portugal, which contribute EEG and ECG data from long-term monitoring of epilepsy patients as well as standardized annotations and clinical metadata.

Study population

ECG recordings of patients were compiled as part of the EPILEPSIAE project (38). The EEG/ECG data have been registered during long-term pre-surgical monitoring. During recording, each patient had at least three clinically manifest seizures with interictal intervals of >4 h.

The sampling rate of data was 1024 Hz and filtered for line noise at 50 Hz. Clinical features of epileptic patients are listed in Table 1. The total number of 133 seizures were collected from 12 patients (seven males and five females; mean age 43.91 years, SD: 10.16 years) affected by various kinds of epilepsy were admitted to this study. In all cases, EEG was recorded to confirm the seizure onset. None of selected patients had any arrhythmias, congestive heart failure, coronary artery disease or diabetes mellitus.

Two main criteria were considered for choosing the patients: the patients were chosen with the seizure intervals more than four hours in order to have secure borders to select the free-seizure segments far enough from the seizure to avoid the effects of seizure on HRV. The second criterion was based on the assessment of HRV during the day and night. As the heart rate (HR) variables have different values in day and night, the patients who have seizures during the day were selected, and the HRV segments were chosen only from day parts of ECG recordings.

Time domain analysis

HRV has been traditionally analyzed by time domain measures. The simplest and most often used are the instantaneous heart rate (HR), intervals between normal successive sinus beats (i.e., intervals between normal-to-normal QRS complexes, usually referred to with the abbreviation NN), average HR, mean NN interval, and the difference between the longest and shortest NN interval.

HRV is analyzed using both linear and nonlinear features. In this study, the HRV signals were analyzed using EPILAB; a MATLAB® toolbox (Author-provide manufacturer name and country), for epileptic seizure prediction that allows studying epileptic seizures based on a high dimensional feature space (39). The 48-hour ECG data were collected and analyzed in different segments. These segments started from three hours before the seizure onset. We analyzed 240, 90-30, 30-10, 10-5 and 5 minutes before the seizure to find changes in HRV signals. In order to analysis HRV, a series of time-domain measures was calculated:

Triangular index

To calculate the triangular index, the RR intervals are ordered into bins thus creating a histogram. The index is calcu-

lated by dividing the integral (area) of the distribution by its maximum height. Thus, RR distributions with greater variability will have a larger spread and thus a smaller peak, the area to peak ratio will be larger than in case of a low variability. Triangular index had a high correlation with the standard deviation of all RR intervals.

Frequency domain analysis

HRV can be categorized into high-frequency power (HF; 0.15-0.40 Hz) and low-frequency power (LF; 0.04-0.15 Hz), both of which depend on oscillatory frequency and development mechanism.

The LF and HF components of HRV were identified by power spectral analysis, using Fast Fourier Transform (FFT). The LF component is influenced by both parasympathetic and sympathetic regulation. The HF component and LF/HF ratio reflect the extent of vagal (parasympathetic) and sympathetic regulation of the heart, respectively (40).

Non-linear method-Poincaré plot

One of the methods used to look at cardiac function is the Poincaré plot. The Poincaré plot is a popular two-dimensional visualization tool for dynamic systems due to its intuitive display of the dynamic properties of a system from a time series. It is known as return maps or scatter plots where the current RR value is plotted against the following RR value. A graphical presentation of RR can be produced with SD1 as the short-term variability and SD2 as the long-term variability.

SD2 is defined as the standard deviation of the projection of the Poincaré plot on the line of identity (y=x), and SD1 is the standard deviation of projection of the Poincaré plot on the line perpendicular to the line of identity (41). Both parameters can be defined as:

$$SD1 = \sqrt{Var(x1)}[ms; ms], SD2 = \sqrt{Var(x2)}[ms; ms] \quad (1)$$

Where $Var(x)$ is the variance of x, and

$$x_1 = \frac{\overrightarrow{RR_i} - \overrightarrow{RR_{i+1}}}{\sqrt{2}}, x_2 = \frac{\overrightarrow{RR_i} + \overrightarrow{RR_{i+1}}}{\sqrt{2}}[ms; ms; ms] \quad (2)$$

$\overrightarrow{RR_i}$ and $\overrightarrow{RR_{i+1}}$ are vectors defined as:

$$\overrightarrow{RR_i} = (RR_1, RR_2, \ldots, RR_{N-1}) \quad (3)$$
$$\overrightarrow{RR_{i+1}} = (RR_2, RR_3, \ldots, RR_N)$$

In the other words it means, that x_1 and x_2 correspond to the rotation of $\overrightarrow{RR_i}$ and $\overrightarrow{RR_{i+1}}$ by angle $\frac{\pi}{4}$:

$$\begin{bmatrix} x_1 \\ x_2 \end{bmatrix} = \begin{bmatrix} \cos\frac{\pi}{4} & -\sin\frac{\pi}{4} \\ \sin\frac{\pi}{4} & \cos\frac{\pi}{4} \end{bmatrix} \cdot \begin{bmatrix} RR_i \\ RR_{i+1} \end{bmatrix} \quad (4)$$

SD1 has been correlated with high frequency power while SD2 has been correlated with both low and high frequency powers. The ratio SD2/SD1 is associated with the randomness of the HRV signal. It has been suggested that the ratio SD2/SD1, which is a measure of the randomness in HRV time series, has the strongest association with mortality in adults (42). However, the increased SD2/SD1 values over time suggest a higher level of randomness is present in HRV. A sample comparison of return map for 5 and 30-10 minutes before the seizure is represented in Figure 1.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 19 (IBM, Armonk, NY, USA). As data was symmetrically distributed, paired t-test test was used to evaluate whether there was a significant relationship between the heart rate changes and pre-ictal phase during the event progression for each individual seizure, within each epoch. Values are given as mean±SD and a p value less than 0.05 was considered as statistically significant.

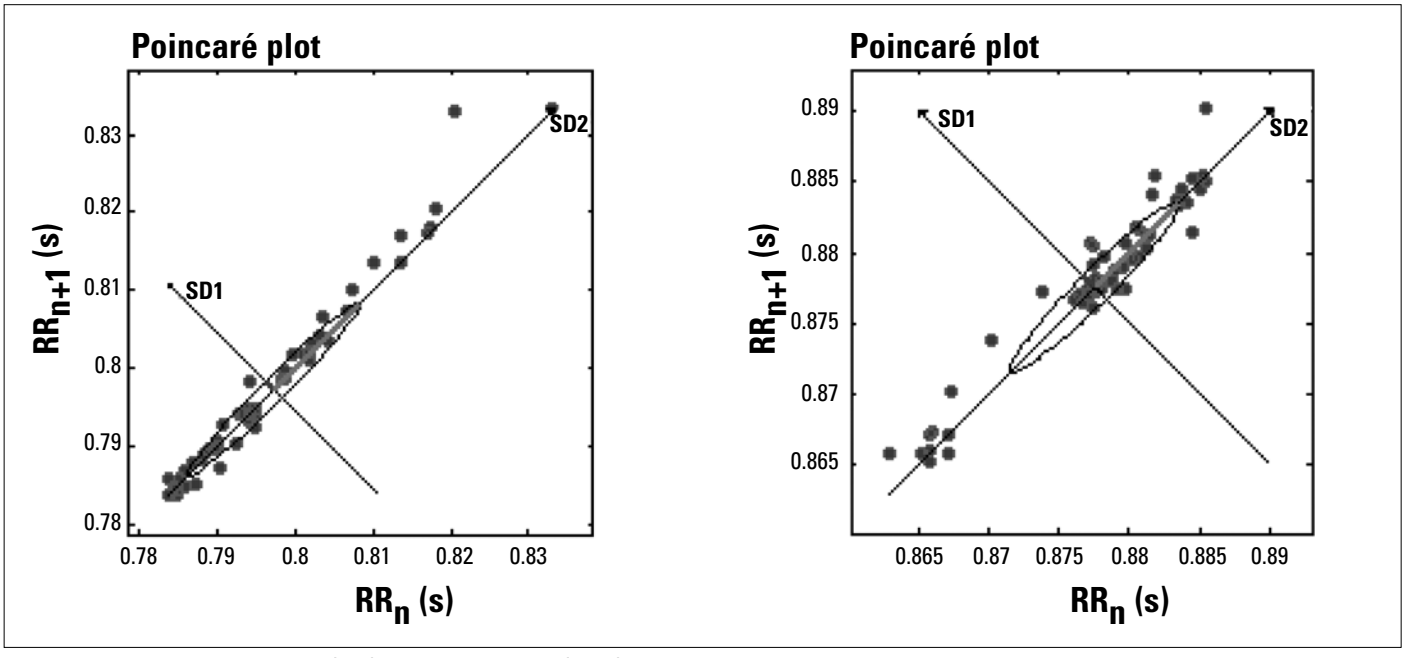

Figure 1. Sample return map for 5 (left) and 30-10 minutes (right) before one of the seizures

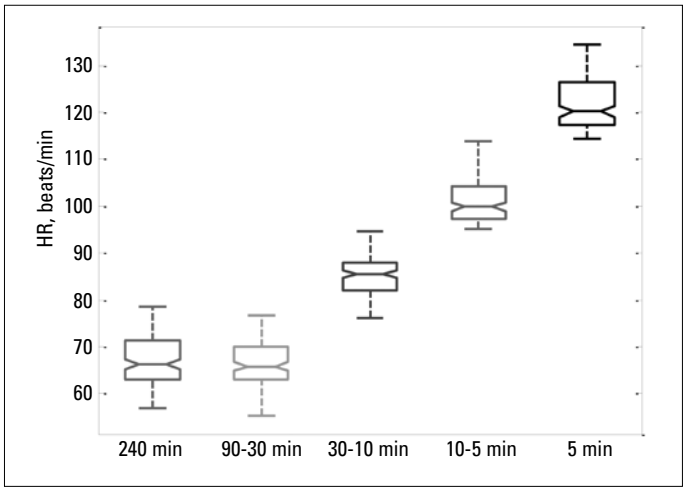

Figure 2. HR comparison in segments before the seizures
HR - heart rate

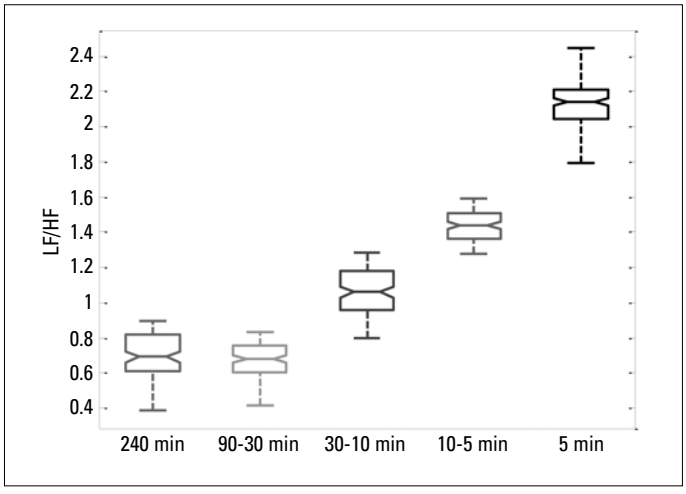

Figure 3. LF/HF ratio comparison in segments before the seizures
HF- high-frequency power, LF- low-frequency power

Results

Tables 2, 3 show the results for all of the features in different segments. In these tables, the percentage of increase, decrease or no significant changes for the total number of 133 epileptic seizures in 12 studied patients is presented. The highest number of changes for each feature is marked in bold.

Figures 2-4 illustrate mean HR, LF/HF and SD2/SD1 for 133 seizures. Segments include the 240, 90-30, 30-10, 10-5 and 5 minutes before the seizures respectively. The results show that mean HR of the patients start to increase from 30 minutes before the seizure and the most increase of mean HR occurred 5 minutes before the seizure (82.7% increase in mean HR).

Triangular index was noted to be decreased during the interictal phase. The results show most decrease in those segments that are closer to the seizure.

The results present a significant increase of LF/HF ratio (2.12±0.5) relative to baseline (0.78±0.24) in 5 minutes before the seizure, which indicates a shift in autonomic balance from the parasympathetic to sympathetic.

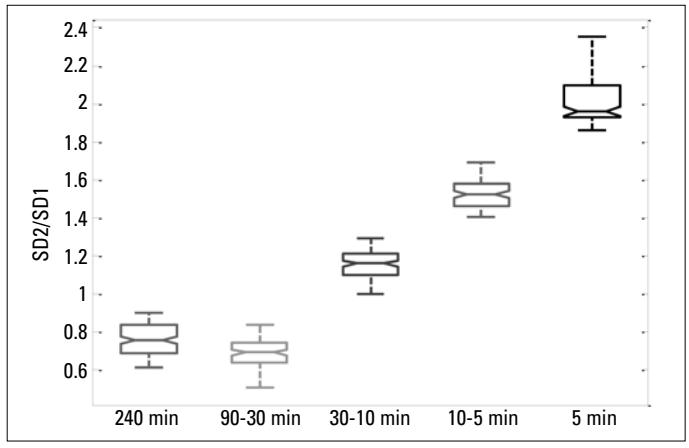

Figure 4. SD2/SD1 comparison in segments before the seizures
SD2 - standard deviation of the projection of the Poincaré plot on the line of identity (y=x), SD1 - standard deviation of projection of the Poincaré plot on the line perpendicular to the line of identity

In addition, SD2/SD1 ratio reflects non-linear information of HRV. We found significant changes in SD2/SD1 ratio started from 30 minutes before the seizure (1.2±0.15), which was most likely due to reduced parasympathetic and enhanced sympathetic cardiac tone. The most increase was seen in 5 minutes before the seizure which shows an increase of 2.03±0.55 in comparison with baseline (0.78±0.14).

Discussion

The aim of this study is to analyze the behavior of pre-ictal segments of ECG to find appropriate features (extracted from time-frequency and non-linear analysis) for designing accurate epileptic seizures detection and prediction system. Significant increase of mean HR was started from 30 minutes before the seizure. Most consistent changes were observed in Mean HR, LF/HF and SD2/SD1, suggesting reduced parasympathetic regulation of heart rate in segments near the seizure. In fact, as LF and SD2 increase and HF and SD1 decrease, their ratio (LH/HF and SD2/SD1) increases as well indicating a shift in vagal and sympathetic activities, with a shift in balance toward relative sympathetic enhancement. Our findings support the concept that closer segments to the seizure represent a continuum of increasing sympathetic dominance to those segments away from the seizure. Our results indicate that during pre-ictal period of seizures, increase of sympathetic and inhabitation of parasympathetic function occurs in most of epileptic seizures regardless of epileptic type; especially in closer segments to the seizure (5 minutes).

Early recognition of autonomic nervous system dysfunction could prevent potentially dangerous dysrhythmias. Furthermore, the identification of patients with certain epilepsy characteristics, which make them more vulnerable to cardiovascular symptoms than others, would be important for prognosis and treatment issues.

Over the last decade, some researches have been done to assess the pre-ictal phase with short-term HRV analysis. There are reports of rising LF and HF power amplitude just some min-

Table 1. Information of 12 studied patients

ID	Sex	Age	Seizure type	Localization	Num. of seizure	Rec. time (h)
1	M	47	CP, UC	T	6	93.68
2	F	37	CP, SP, UC	T	11	243.72
3	F	62	CP	T	6	164.43
4	F	35	CP	P	9	158.41
5	M	31	CP, SP, UC	F	15	163.98
6	F	54	CP, UC	T	10	94.38
7	M	58	CP, UC	T	9	160.39
8	M	46	SG, UC	F	7	68.97
9	F	34	SG, SP	F	11	133.79
10	M	48	CP, SPf	T	14	237.63
11	M	39	CP, SP, UC	T	30	113.83
12	M	36	SP	T	5	118.27
Total					133	1751.48

F - frontal, P - parietal, T - temporal
CP - complex partial, SG - secondarily generalized, SP - simple partial, UC - unclassified
Rec - recording

Table 2. HR parameters for the 12 studied patients including 133 seizures

	Time before the seizure, minute					
Feature	**240 min**	**90-30 min**	**30-10 min**	**10-5 min**	**5 min**	***p**
Mean HR, beats·min^{-1}	66.52±11.7	65.32±11.69	85.35±17	98.17±22.55	119.36±30.82	*0.0207
Triangular index	0.06±0.004	0.06±0.004	0.05±0.004	0.04±0.004	0.03±0.004	0.31
LF/HF, ms^2/ms^2	0.78±0.24	0.77±0.25	1.1±0.22	1.53±0.33	2.12±0.5	*0.0332
SD2/SD1 ratio	0.78±0.14	0.7±0.12	1.2±0.15	1.65±0.36	2.03±0.55	*0.0431

Heart rate parameters are presented by mean and standard deviation;
paired t-test p<0.05
HR (min^{-1}) - heart rate, HF (ms^2) - power in high frequency range (0·15-0·4 Hz), LF (ms^2) - power in low frequency range (0·04-0·15 Hz), SD - standard deviation

Table 3. Results for the 12 studied patients including 133 seizures

Time before the seizure (minute)	Mean HR (beats·min^{-1})			Triangular index			LF/HF			SD2/SD1 (ms^2/ms^2)		
	Inc.↑	Dec.↓	NSC	Inc.↑	Dec.↓	NSC	Inc.↑	Dec.↓	NSC	Inc.↑	Dec.↓	NSC
240 min	(26.31%)	15.03%	58.66%	14.28%	16.54%	69.18%	18.79%	14.28%	66.93%	10.52%	13.53%	75.95%
90-30 min	(30 %)	13.53%	56.47%	12.78%	17.29%	69.93%	26.31%	16.54%	57.15%	16.54%	17.29%	66.17%
30-10 min	70.15%	16.31%	13.54%	21.05%	24.81%	54.14%	73.6%	7.59%	18.81%	79.09%	10.07%	10.84%
10-5 min	76.69%	16.54%	6.77%	33.83%	45.11%	21.06%	78.19%	16.54%	5.27%	73.68%	21.05%	5.27%
5 min	82.7%	8.27%	9.03%	30.07%	55.63%	14.3%	81.95%	12.78%	5.27%	81.2%	10.52%	8.28%

Dec. - decreasing in value, Inc. - increasing in value, NSC - no significant changes

utes before seizure onset with HF power peak about 30 sec pre seizure onset followed by a rapid decline and minimum reach during seizure in temporal lobe and complex partial seizures (42). Another study concerning seizure detection of newborn children found a HF power drop during seizure (43). Although there are some reports of HRV changes in pre-ictal phase, still there is not any concentrated study on the effects of epileptic seizures on the cardiovascular system and epilepsy-related alteration of sympathetic and parasympathetic balance.

On the other hand, with respect to nonlinear HRV analysis, to the best of our knowledge, only a few research groups applied nonlinear HRV on epilepsy patients and unfortunately, these researches are restricted to special types of epilepsy like temporal lobe or refractory epilepsy (10, 16, 44-48). It is important to note that nonlinear HRV techniques will not replace linear analysis, but have to be considered as a completion. Nonlinear techniques have the advantage over linear techniques in providing better repeatability and reliability across measurements. Therefore, nonlinear indices may be more suitable for diagnostic purposes, as well as for assessing individual treatment effects (49).

Study limitations

The limitations of our study were small number of patients studied from each type of seizures; therefore, there was lack of analysis of epileptic type's effects on HRV parameters of pre-ictal periods. In addition, we did not investigate the effect of age and gender of patients, and localization and lateralization of epileptic seizures on autonomic dysfunction. That is why new studies must be done in order to define mentioned factor's effect on the HRV parameters. In addition, future work may include researching for other features to better analyze the behavior of HRV in different stages of epileptic seizures in day/night.

Conclusion

HRV analysis is a valid method for quantifying central influences on autonomic cardiac changes, and can give valuable information when used as an adjunct during clinical seizures. A major advantage of ECG-based seizure detection is that the ECG is an inherently easier signal to acquire, with a higher signal to noise ratio to that of EEG and can be recorded on a single channel.

The findings of current research paper might represent an important factor contributing to the complex mechanism of SUDEP, which takes place most often in patients with epileptic seizures. This suggests that the study of ECG in epileptic patient's activity can be a key to find patterns of autonomic changes in epileptic seizure. In fact, cardiac autonomic changes can act as a marker for brain processes associated with epileptic seizure expression. We believe that these features are convenient for clinical use. We are now in the process of working with physicians to find more features for detection and prediction of epileptic seizures using cardiac information.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - S.B.; Design - S.B.; Supervision - N.J.D., A.M.N.; Resource - C.A.T., A.D.; Materials - C.A.T., A.D.; Data collection&/or Processing - C.A.T., A.D.; Analysis &/or interpretation - S.B.; Literature search - S.B.; Writing - S.B.; Critical review - C.A.T., A.D.; Other - S.B.

Acknowledgment: We sincerely thank to Mr. Mohammad Karimi Moridani for his most support and encouragement at different stages of developing this paper. This work was partially funded by the European Project EPILEPSIAE (EU FP7 Grant 211713) and ICIS project CENTRO-07-0224-FEDER-002003.

References

1. Epilepsy Facts and Figures. Landover. Epilepsy Foundation of America, 1999.
2. Litt B, Esteller R, Echauz J, D'Alessandro M, Shor R, Henry T, et al. Epileptic seizures may begin hours in advance of clinical onset: A report of five patients. Neuron 2001; 30: 51-64. [CrossRef]
3. Clercq W De, Lemmerling P, Van Huffel S, Van Paesschen W. Evaluation of methods for determining a pre-ictal state in scalp-EEG measurements, In Proceeding of International Federation for Medical and Biological Engineering (*IFMBE*) 2000; 3: 446-7.
4. Iasemidis LD, Pardalos P, Sackellares JC, Shiau DS. Quadratic binary programming and dynamical system approach to determine the predictability of epileptic seizures. J Comb Optim 2001; 5: 9-26. [CrossRef]
5. Jerger KK, Netoff TI, Francis JT, Sauer T, Pecora L, Weinstein SL, et al. Early seizure detection. J Clin Neurophysiol 2001; 18: 259-68. [CrossRef]
6. Lehnertz K, Andrzejak RG, Arnhold J, Kreuz T, Mormann F, Rieke C, et al. Nonlinear EEG analysis in epilepsy: it's possible use for interictal focus localization, seizure anticipation, and prevention. J Clin Neurophysiol 2001;18: 209-22. [CrossRef]
7. Le Van Quyen M, Adam C, Martinerie J, Baulac M, Clemenceau S, Varela F. Spatio-temporal characterizations of non-linear changes in intracranial activities prior to human temporal lobe seizures. Eur J Neurosci 2000; 12: 2124-34. [CrossRef]
8. Le Van Quyen M, Martinerie J, Navarro V, Boon P, D'Have M, Adam C, et al. Anticipation of epileptic seizures from standard EEG recordings. Lancet 2001; 357: 183-8. [CrossRef]
9. Navarro V, Martinerie J, Le Van Quyen M, Clemenceau S, Adam C, Baulac M, et al. Seizure anticipation in human neocortical partial epilepsy. Brain 2002; 125: 640-55. [CrossRef]
10. Ansakorpi H, Korpelainen JT, Huikuri HV, Tolonen U, Myllyla VV, Isojarvi JI. Heart rate dynamics in refractory and well controlled temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 2002; 72: 26-30. [CrossRef]
11. Ansakorpi H, Korpelainen JT, Tanskanen P, Huikuri HV, Koivula A, Tolonen U, et al. Cardiovascular regulation and hippocampal sclerosis. Epilepsia 2004; 45: 933-9. [CrossRef]
12. Darbin O, Casebeer D, Naritoku DK. Effects of seizure severity and seizure repetition on postictal cardiac arrhythmia following maximal electroshock. Exp Neurol 2003; 181: 327-31. [CrossRef]
13. Devinsky O, Perrine K, Theodore WH. Interictal autonomic nervous system functions in patients with epilepsy. Epilepsia 1994; 35: 199-204. [CrossRef]
14. Frysinger RC, Engel J, Harper RM. Interictal heart rate patterns in partial seizure disorders. Neurology 1993; 43: 2136-9. [CrossRef]
15. Naritoku DK, Casebeer DJ, Darbin O. Effects of seizure repetition on postictal and interictal neurocardiac regulation in the rat. Epilepsia 2003; 44: 912-6. [CrossRef]
16. Ronkainen E, Ansakorpi H, Huikuri HV, Myllyla VV, Isojarvi JI, Korpelainen JT. Suppressed circadian heart rate dynamics in temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 2005; 76: 1382-6. [CrossRef]
17. Stein PK, Reddy A. Non-linear heart rate variability and risk stratification in cardiovascular disease. Indian Pacing Electrophysiol J 2005; 5: 210-20.

18. Evrengül H, Tanrıverdi H, Dursunoğlu D, Kaftan A, Kuru O, Ünlü U, et al. Time and frequency domain analyses of heart rate variability in patients with epilepsy. Epilepsy Res 2005; 63: 131-9. [CrossRef]
19. Kamath MV, Upton AR, Talalla A, Fallen EL. Effect of vagal nerve electro stimulation on the power spectrum of heart rate variability in man. Pacing Clin Electrophysiol 1992; 15: 235-43. [CrossRef]
20. Kuo TB, Lin T, Yang CC, Li CL, Chen CF, Chou P. Effect of aging on gender differences in neural control of heart rate. Am J Physiol 1999; 277: H2233-9.
21. Liu CC, Kuo TB, Yang CC. Effects of estrogen on gender-related autonomic differences in humans. Am J Physiol Heart Circ Physiol 2003; 285: H2188-93.
22. Lucreziotti S, Gavazzi A, Scelsi L, Inserra C, Klersy C, Campana C, et al. Five-minute recording of heart rate variability in severe chronic heart failure. Correlates with right ventricular function and prognostic implications. Am Heart J 2000; 139: 1088-95. [CrossRef]
23. Wang JD, Kuo TB, Yang CC. An alternative method to enhance vagal activities and suppress sympathetic activities in humans. Auton Neurosci 2002;100: 90-5. [CrossRef]
24. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996; 93: 1043-65. [CrossRef]
25. Ansakorpi H, Korpelainen JT, Suominen K, Tolonen U, Myllylä VV, Isojärvi JI. Interictal cardiovascular autonomic responses in patients with temporal lobe epilepsy. Epilepsia 2000; 41: 42-7. [CrossRef]
26. Massetani R, Strata G, Galli R, Gori S, Gneri C, Limbruno U, et al. Alteration of cardiac function in patients with temporal lobe epilepsy. Different roles of EEG-ECG monitoring and spectral analysis of RR variability. Epilepsia 1997; 38: 363-9. [CrossRef]
27. Nouri S, Balish M, Devinsky O. Epilepsy and the autonomic nervous system. eMedicine Journal 2001; 2: 155.
28. Novak V, Reeves AL, Novak P, Low PA, Sharbrough FW. Time-frequency mapping of R-R interval during complex partial seizures of temporal lobe origin. J Auton Nerv Syst 1999; 77: 195-202. [CrossRef]
29. Delamont RS, Julu PO, Jamal GA. Changes in a measure of cardiac vagal activity before and after epileptic seizures. Epilepsy Res 1999; 35: 87-94. [CrossRef]
30. Isojärvi JI, Ansakorpi H, Suominen K, Tolonen U, Repo M, Myllylä VV. Interictal cardiovascular autonomic responses in patients with epilepsy. Epilepsia 1998; 39: 420-6. [CrossRef]
31. Frysinger RC, Engel J, Harper RM. Interictal heart rate patterns in partial seizure disorders. Neurology 1993; 43: 2136-9. [CrossRef]
32. Massetani R, Strata G, Galli R, Gori S, Gneri C, Limbruno U, et al. Alteration of cardiac function in patients with temporal lobe epilepsy: different roles of EEG-ECG monitoring and spectral analysis of RR variability. Epilepsia 1997; 38: 363-9. [CrossRef]
33. Tomson T, Ericson M, Ihrman C, Lindblad LE. Heart rate variability in patients with epilepsy. Epilepsy Res 1998; 30: 77-83. [CrossRef]
34. Thakor NV, Pan K. Tachycardia and fibrillation detection by automatic implantable cardioverter defibrillators: sequential testing in time domain. IEEE Eng Med Biol Mag 1990; 9: 21-4. [CrossRef]
35. Guzik P, Piskorski J, Krauze T, Schneider R, Wesseling KH, Wykretowicz A, et al. Correlations between the Poincaré Plot and conventional heart rate variability parameters assessed during paced breathing. J Physiol Sci 2007; 57: 63-71. [CrossRef]
36. Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. Am J Physiol Heart Circ Physiol 2000; 278: 2039-49.
37. Annegers JF, Coan SP. SUDEP: overview of definitions and review of incidence data. Seizure 1999; 8: 347-52. [CrossRef]
38. Ihle M, Feldwisch-Drentrup H, Teixeira CA, Witon A, Schelter B, Timmer J, et al. A European epilepsy database. EPILEPSIAE Comput Methods Programs Biomed 2010; 106: 127-38. [CrossRef]
39. Teixeira CA, Direito B, Feldwisch-Drentrup H, Valderrama M, Costa RP, Alvarado-Rojas C, et al. EPILAB: a software package for studies on the prediction of epileptic seizures. J Neurosci Methods 2011; 200: 257-71. [CrossRef]
40. Perini R, Orizio C, Baselli G, Gerutti S, Veicsteinas A. The influence of exercise intensity on the power spectrum of heart rate variability. Eur J Appl Physiol Occup Physiol 1990; 61: 143-8. [CrossRef]
41. Piskorski J, Guzik P. Filtering Poincaré plot. Comput Method Sci Technol 2005; 11: 39-48.
42. Novak VV, Reeves LA, Novak P, Low AP, Sharbrough WF. Time-frequency mapping of RR interval during complex partial seizures of temporal lobe origin, J Auton Nerv Syst 1999; 77: 195-202. [CrossRef]
43. Malarvili MB, Mesbah M. Newborn seizure detection based on heart rate variability. IEEE Trans Biomed Eng 2009; 56: 2594-603. [CrossRef]
44. Ronkainen E, Korpelainen JT, Heikkinen E, Myllyla VV, Huikuri HV, Isojarvi JI. Cardiac autonomic control in patients with refractory epilepsy before and during vagus nerve stimulation treatment: a one-year follow-up study. Epilepsia 2006; 47: 556-62. [CrossRef]
45. Jansen K, Vandeput S, Milosevic M, Ceulemans B, Van Huffel S, Brown L, et al. Autonomic effects of refractory epilepsy on heart rate variability in children: influence of intermittent vagus nerve stimulation. Dev Med Child Neurol 2011; 53: 1143-9. [CrossRef]
46. Cadeddu C, Deidda M, Mercuro G, Tuveri A, Muroni A, Nocco S, et al. Cardiovascular modulation during vagus nerve stimulation therapy in patients with refractory epilepsy. Epilepsy Res 2010; 92: 145-52. [CrossRef]
47. Lotufo PA, Valiengo L, Benseñor IM, Brunoni AR. A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs. Epilepsia 2012; 53: 272-82. [CrossRef]
48. Milosevic M, Vandeput S, Van Huffel S, Jansen K, Lagae L. Heart Rate Variability Analysis of Children with Refractory Epilepsy before and after the Vagus Nerve Stimulation. In Proceeding of the International Conference on Bio-inspired Systems and Signal Processing (BIOSTEC) 2011; 409-12.
49. Maestri R, Pinna GD, Porta A, Balocchi R, Sassi R, Signorini MG, et al. Assessing nonlinear properties of heart rate variability from short-term recordings: are these measurements reliable? Physiol Meas 2007; 28: 1067-77. [CrossRef]