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ORIGINAL ARTICLE

Ictal Heart Rate Variability Assessment with Focus on Secondary Generalized and Complex Partial Epileptic Seizures

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ABSTRACT
The purpose of present study was to analyze the effects of epilepsy on the autonomic control of the heart in ictal phase of Secondary Generalized (SG) and Complex Partial (CP) epileptic seizures in order to find an algorithm for classification of epileptic and non-epileptic classes. Fifteen patients with epilepsy (eight males and seven females; mean age 42.2 years, SD: 12.64 years)comprising 96 secondary generalized seizures (six patients), 110 complex partial seizures (nine patients) were selected for this study. One lead ECG recordings of patients with epilepsies were compiled through long-term monitoring of epilepsy patients. HRV signal with duration of 5 minute, randomly cut out from seizure-free (five hours before the seizure) and seizure activities of both groups of epileptic patients were chosen to analysis of HRV in both kinds of epileptic seizure. A set of Time and Frequency domain and nonlinear parameters extracted from HRV is analyzed. 206 seizures were analyzed from fifteen patients. There was evidence for the increase of sympathetic in ictal phase of both SG and CP seizures, which significantly differ from seizure-free segments. There was a significant increase in Mean HR, LF/HF and SD2/SD1 ratio of SG when compared to same features of CP. Also there was significant decrease of R-R intervalsand S in SG seizurescompare to CP seizures. Our results indicate that there are a significant differences between autonomic behaviors of CP and SG subjects. Comparison of HR variables between two groups of epileptic patients during ictal phase indicates that SG seizures show more sympathetic activity in comparison with CP seizures. It can be conclude that the degree of autonomic nervous system (ANS) dysfunction can be related to the type of epileptic seizure.
Keywords: Epileptic Seizure, Complex Partial, Secondary Generalized, Ictal, HRV

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INTRODUCTION

Epilepsy is a chronic disorder of central nervous system that predisposes individuals to experiencing recurrent seizures [1]. A seizure is a sudden, transient aberration in the brain's electrical activity that produces disruptive symptoms. These symptoms range between a lapse in attention, a sensory hallucination, or a whole-body convulsion [2].Epilepsy is divided into several categories with more differences in the characteristics of the electrical discharges as well as the clinical manifestations. In 1981, the International League against Epilepsy (ILAE) formulated an international classification of epileptic seizures that divided seizures into two major classes: partial seizures and generalized seizures [3]. This classification is based on clinical and electroencephalographic (EEG) observations of the extent to which the brain is affected by the ictal discharges.

It is well known that epileptic seizures have profound effects on the autonomic nervous system [4-6]. Based on previous studies [7-15], indicators of HRV could be used to predict sudden unexplained death in epilepsy patients(SUDEP)risk and guide epilepsy treatment. It has been hypothesized that SUDEP is primarily due to increased sympathetic regulation[8, 10, 12, 14 and 16-18]. One study reported that increased parasympathetic or vagal activity protected against SUDEP by suppressing atrial or ventricular fibrillation [19]. These results suggested that SUDEP risk was greater in patients with higher sympathetic or lower parasympathetic regulation.

HRV analysis has been applied widely in many clinical studies, including unexpected death, cardiovascular diseases, hypertension, and diabetes [20-22]. The clinical importance of HRV has been known since the publication of studies established that HRV was an independent and strong predictor of mortality after myocardial infarction [23-24]. High-frequency HRV is important to consider because it is associated with vagus nerve and parasympathetic control of the heart, and low values indicate dysfunctional central nervous system control of the cardiac rhythm [25-26]. Low HRV is strongly

predictive of increased mortality in heart disease, and is associated with an increased risk of lethal arrhythmias and unexpected cardiac death[25, 27]. HRV is reduced in people with poorly controlled epilepsy, who are at higher risk for SUDEP [8, 15, 28-32].

In this paper, we will analyze the ictal behaviors of seizures, focusing on complex partial and secondary generalized seizures that induce particularly debilitating behaviors. The aim of this study was to assess and investigate the role of epileptic seizuretypes on central nervous system and the presence and severity of autonomic dysfunction by evaluating time and frequency domain and non-linear analyses of HRV in a series of randomly selected patients who have different types ofseizures.

The purpose of this paper is to evaluate the changes of the HRV using five-minute measuring data to show whether that would differ significantly from the result measured in ictal phase of two types of seizures. These behaviors can lead us to design an efficient classifier to detect and classify different types of seizures from seizure-free segments.

The organization of the paper is as follows. In Section 2, we briefly describe the data set of the ECGsignals used in our study, and then we explain the proposed method for feature extraction with subsections. In Section 3, the experimental results are presented. In section 4, the discussion and conclusion are given.

MATERIALS AND METHODS

Data description

One lead ECG recordings of patients with pharmaco resistant focal epilepsies were compiled as part of the EPILEPSIAE project [33]. 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. The sampling rate of data was 256 Hz and filtered for line noise at 50 Hz.Clinical features of epileptic patients are listed in Table 1. The total number of 206 seizures were collected from fifteen patients (eight males and seven females; mean age 42.2 years, SD: 12.64 years) comprising 96 secondary generalized seizures (six patients with mean duration of 1.97minutes seizure), 110 complex partial seizures (nine patients with mean duration of 1.52minutes) were selected for this study.In all cases, EEG was recorded to confirm the seizure onset.

Two main criteria were considered for choosing the patients: the patients were chosen with the seizure intervals more than five hours to have secure borders to select the seizure-free 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 HR variables have different values in the 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.

Table 1.Clinical features of fifteen studied patients

ID	Sex	Age	Seizure Type	Localization	Number of Seizure	Recording Time (hour)	Avg. Dur.(minute)
1	M	47	CP,UC	T	6	93.68	2.27
2	F	37	CP,SP,UC	T	11	243.72	1.2
3	F	62	CP	T	6	164.43	1.3
4	F	35	CP	P	9	158.41	1.37
5	M	31	CP,SP,UC	F	15	163.98	1.55
6	F	54	CP,UC	T	10	94.38	1.1
7	M	58	CP,UC	T	9	160.39	1.83
8	M	48	CP,SP	T	14	237.63	1.41
9	M	39	CP,SP,UC	T	30	113.83	1.68
10	M	46	SG,UC	F	7	68.97	2.06
11	M	51	SG,SP	T	6	118.5	2.04
12	F	34	SG,SP	F	11	133.79	2.11
13	F	50	SG,UC	T	14	163.04	2.23
14	M	17	SG,SP	T	31	143.34	1.78
15	F	24	SG,SP,UC	F	27	186.64	1.63
Total					**206**	**2244.73**	**Total average(1.7)**

- **SG:** Secondarily Generalized**, SP:** Simple Partial**, CP:** Complex Partial**, UC:** Un-Classified
- **T:** Temporal**, P:** Parietal**, F:**Frontal
- **Avg. Dur. (minute):** Average seizure duration for each patient in minute

Time domain analysis

HRV has been traditionally analyzed by time domain measures. The mean RR interval is an indicator of the ratio of the cardiac sympathetic to parasympathetic tones [34]. In this study, the HRV signals were analyzed using EPILAB; a MATLAB® toolbox, for epileptic seizure prediction that allows studying seizure prediction based on a high dimensional feature space [35]. The HRV features considered in this study, were extracted from 5-minutes non-overlapping segments, which were randomly cut out from continuous ECG recordings. Seizure-free segments contained HRV signal during the intervals far from the seizure (five hours before the seizure),and epileptic segment contained seizure activity. As all the seizures occurred during the day, for each group of seizures (CP and SG), the segments were chosen from day parts of their ECG recordings. The time-domain features used in this study include:

a) Mean HR
b) Mean RR intervals
c) MBPM (Maximum Beat per Minute)

Frequency domain analysis

The HRV is composed by multiple frequencies. The two main frequency components that represent ANS activities are the low frequency (LF) components (0.04 to 0.15Hz) and the high frequency (HF) components (0.15 to 0.4 Hz). Frequency domain analysis confirms that the LF and HF oscillatory components are relative indices of cardiac sympathetic and vagal activity respectively. In this research, parameters obtained based on frequency analysis include:

a) LF
b) HF
c) LF/HF

Non-linear method-Poincaré plot

Poincaré plot analysis is a visual technique to recognize the hidden patterns in a time-series signal. It has been shown to be valuable in various studies [36]and provides similar information to that obtained from spectral HRV analysis. However, Poincaré plot analysis is easier to use than spectral HRV as it does not need special assumptions and data filtering. One advantage of the Poincaré method over spectral analysis techniques is that it is not sensitive to stationary irregularities and trends in RR intervals. Therefore, become more suitable for HRV analyses using ambulatory ECG recordings.

In HRV analysis, Poincaré plot 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.

In our research we want to use the combination of these two measures to form two additional Poincaré plots descriptors. These combinations are:

$S = \pi . SD1 . SD2$and SD2/SD1 ratio. (1)

S corresponds to the area of the ellipse fitted to the Poincaré plot, and the ratio SD2/SD1 was defined, by analogy as LF/HF from spectral HRV analysis. There are some reasons indicate that S illustrates the total HRV, and SD2/SD1 describes sympatho-vagal balance(see [37] for details). S and SD2/SD1, by analogy with LF/HF powers, help to derive additional information from SD1 and SD2 that is not available if these two descriptors are considered separately [37].

In this way, the information obtained from Poincaré plot of HRV is richer than with SD1 and SD2 only, and similar to the one given by the spectral approach to HRV. This seems to be true for two reasons:

1) The influence of changing respiratory frequency on HRV is similarly detected by spectral and Poincaré plot analysis.
2) There are a number of significant correlations between the Poincaré plot descriptors and HRV as well as baroreflex sensitivity [37].

The highest correlation for S has been found with baroreflex sensitivity. It suggests that the area of Poincaré plot represents the total variability of HRV and is under strong vagal influence [39-41].The association of S with other indices of autonomic modulation of heart rate suggests that S is related to parasympathetic tone (HF, RMSSD), reflex vagal activity (BRS), and sympathetic activity (LF).

The best correlation of SD1, measuring short-term HRV, is with baroreflex sensitivity and HF also confirming its known relationship with vagal activity[36, 40, 42-43]. SD2 is more correlated with LF and baroreflex sensitivity, as well as with LF/HF, showing its dependence on both parasympathetic and sympathetic activity [39-41]. Finally, SD2/SD1 is best correlated with LF/HF, which is believed to correspond to the sympatho-vagal balance, then with LF dependent on both branches of ANS and negatively with HF that is commonly used as a measure of parasympathetic tone [39].

The correlation between SD2 and LF is twice as large as with HF, which supports the hypothesis that SD2 is related more strongly to sympathetic than to parasympathetic tone. This conclusion is further supported by a significant correlation between SD2 and LF/HF.It has been suggested that the SD2/SD1 ratio, which is a measure of the randomness in HRV time series, has the strongest association with mortality in adults.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 19 (IBM, Armonk, NY, USA). Continuous, normally distributed data were presented as Mean ±SD. The significance of differences between groups was examined using Student's *t*-test. All statistical assessments were two-sided, and $P < 0.01$ was considered statistically significant.

RESULTS

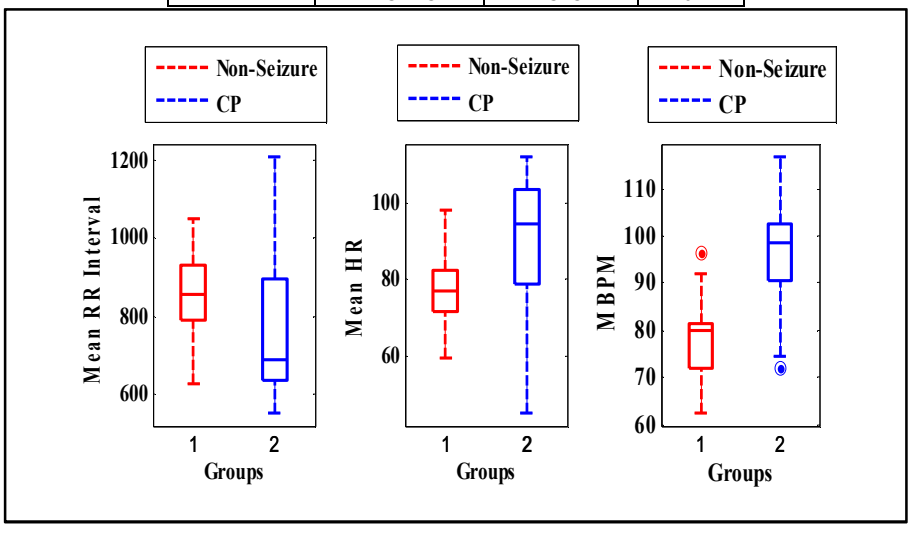
The mean and standard deviation values of HRvariablesfor both groups of patients with CP, SGseizures and seizure-free segments are presented in Table 2 and Table 3 respectively.Time interval between R-R Intervals, were significantly lower during epileptic seizuresin SG (32.86% decrease) compared withCP (20.11% decrease) seizure. Statistical analysis demonstrated that the SG group exhibited lower mean RR intervals, as well as a meaningfully higher mean HR and MBPM, compared with the CP group. Therefore, this results show greater sympathetic activation in SGthan in CP seizuressuggesting a predominance of the sympathetic modulation of the heart.

Table 2. Comparison of HR variables between seizure-free and CP seizures

Feature	Seizure Free	CP	P value
RR (ms)	855.79±19	683.07±23.78	p=0.31
Mean HR	77.21±2.03	88.37±10.4	P=0.26
MBPM	80.23±4.96	96.42±10.30	P=0.02
LF (ms2)	137.2±39.2	178.8±19.5	P=0.38
HF (ms2)	182.2±72	148.9±16.5	P=0.3
LF/HF	0.88±1.4	1.32±2.3	P=0.32
SD1	27.17±30.1	22.93±32	P=0.4
SD2	24.22±5.9	27.59±10.4	P=0.32
SD2/SD1	1.15±0.36	1.36±0.23	P=0.35
S	3.75±13.3	2.2±7.2	P=0.37

Table 3. Comparison of HR variables between seizure-free and SG seizures

Feature	Seizure Free	SG	P value
RR (ms)	852.51±19	572.9±12.7	P=0.21
Mean HR	71.4±2.03	110.33±7.3	P=0.12
MBPM	78.83±3.60	128.74±5.51	P=0.01
LF (ms2)	176.16±39.2	307.1±21.3	P=0.16
HF (ms2)	262.32±52	197.2±40	P=0.24
LF/HF	0.72±1.5	2.14 ± 1.48	P=0.19
SD1	63.40±10.1	48.94±3.4	P=0.23
SD2	60.04±11.9	96.64±3	P=0.136
SD2/SD1	0.87±0.46	1.07±0.54	P=0.21
	2.43±2.3	1.73±3.1	P=0.11



a) b) c)

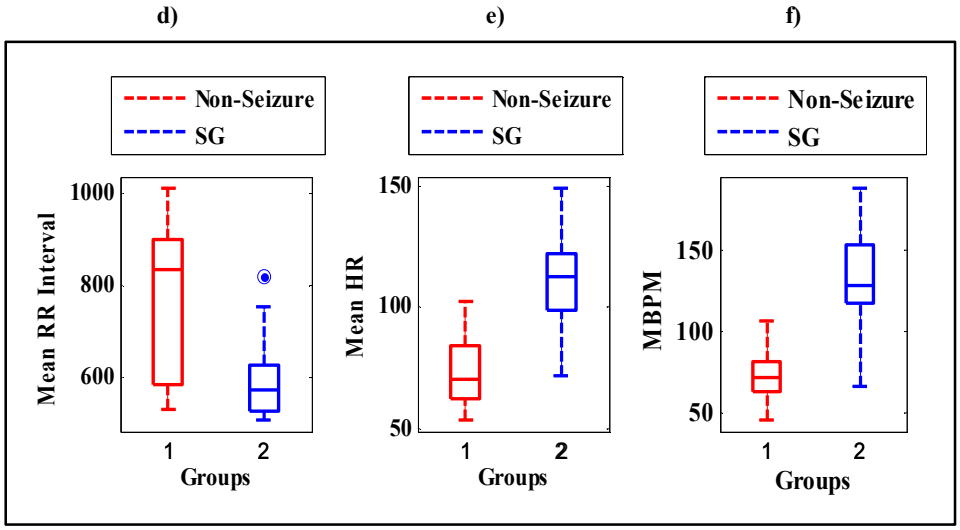


Figure 1. Comparison of RR intervals, HR and MBPM for seizure-free, CP (a, b and c, respectively) and SG (d, e and f respectively) seizures

CP and SG show respectively mean decrease of RR interval from 855.79±19 to683.07±23.78 (p = 0.31)and 852.51±19 to 572.9±12.7 (p = 0.21) indicatingan increase of heart rate.SG seizures led to higher ictal HR in comparison with CP seizures. In CP seizures, increase of HR, were observed in 80/110 (72.72%) attacks while significant HRV changes were observed in 78/110 seizures: tachycardia was seen in 64/110 (58.18%) and bradycardia in 14/110 (12.72%). The mean tachycardia rate was 115beats/minute.

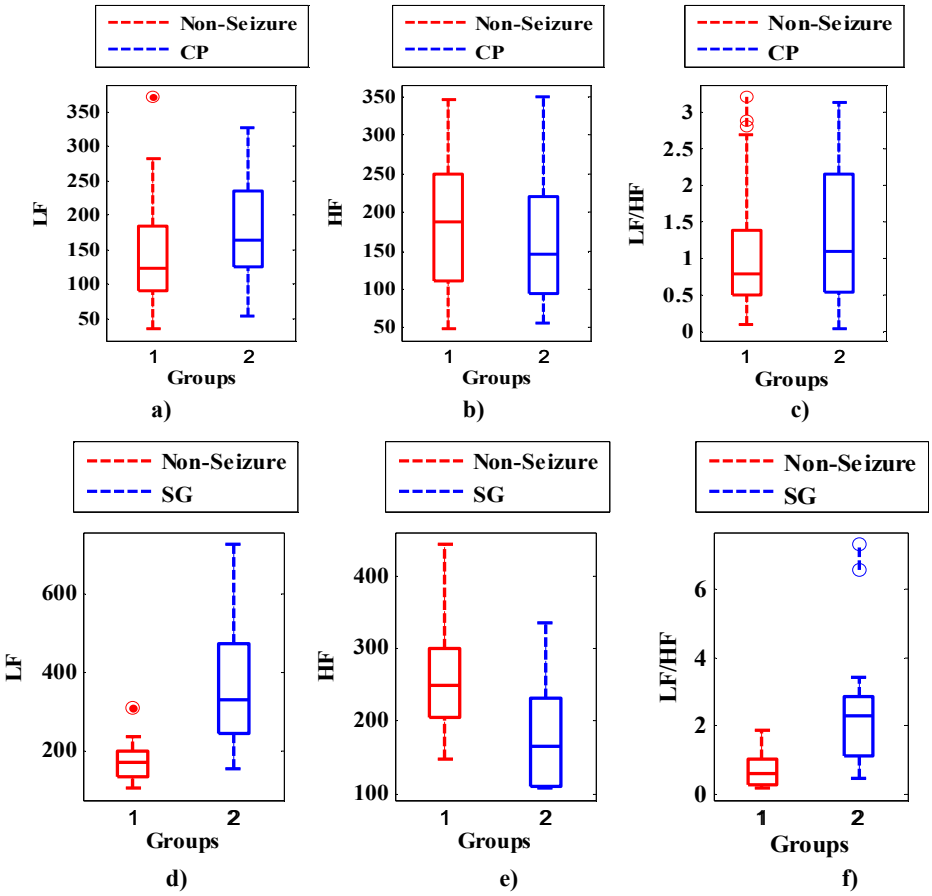


Figure 2. Comparison of LF, HF and LF/HF for seizure-free, CP (a, b and c, respectively) and SG (d, e and f respectively) seizures

In SG seizures, increase of HR, were observed in 78/96 (81.25%) attacks while significant HRV changes were observed in 76/96 seizures: tachycardia was seen in 71/96 (73.95%) and bradycardia in 5/96 (5.2%).

Moreover, the results demonstrate lower, HF, SD1 and S in patients with SG epilepsy compared to patients with CP seizures.The spectral components of HF (p=0.3), Poincaré components of SD1 (p=0.4) and S (p=0.37) were lower in CP than seizure-free HR signals (Figure 2(a, b and c) and Figure 3(a, b, c and d)).

The spectral components of HF (p=0.24) and Poincaré components of SD1 (p=0.23) were lower, and mean of S (p=0.11) show a decrease in SG compared with seizure-free HR signals (Figure 2(d, e and f) and Figure 3(e, f, g and h)). Furthermore, LF, SD2, the LF/HF and SD2/SD1 were increased in both groups of seizures compared with the seizure-free segments.

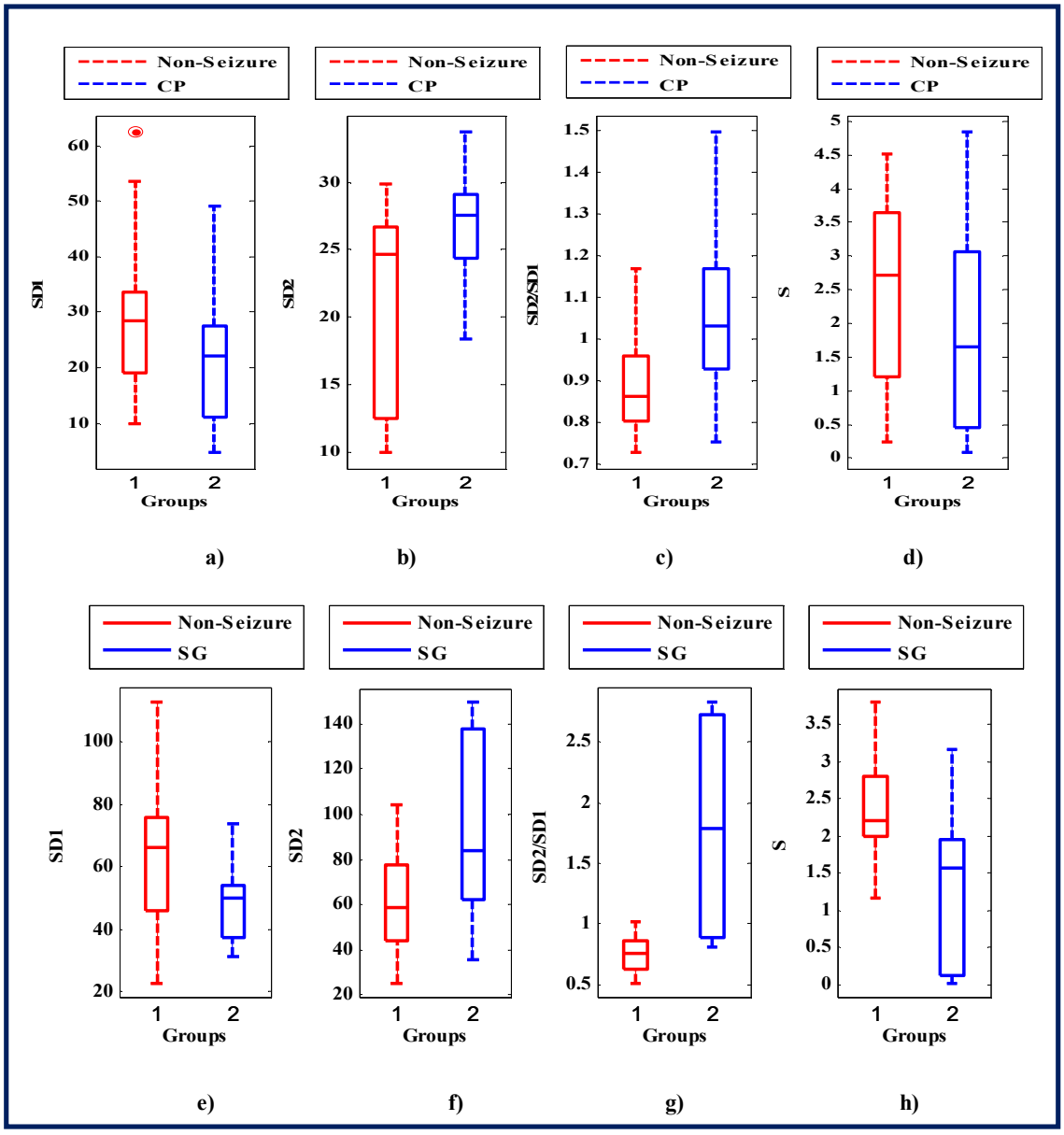


Figure 3. Comparison of SD1, SD2, SD2/SD1 ratio and S for seizure-free, CP (a, b, c and d respectively) and SG (e, f, g and h respectively) seizures

DISCUSSION AND CONCLUSION

Activation of the autonomic nervous system is a well-known ictal phenomenon in patients with epilepsy. Seizures can cause long-term and often progressive cardiac autonomic dysfunction [8, 44].Autonomic dysfunction could be caused by uncontrolled electrical stimulation and chronic

functional changes in the related neuroanatomical regions of the brain. Therefore, SUDEP remains an important cause of mortality in epileptic seizures[45-46].

Heart rate variability analysis revealed both sympathetic and parasympathetic abnormalities in patients. In this article, we compared short-term HRV measures computed during ictal phase in complex partial and secondary generalized seizures.For analysis in the time and frequency domain and non-linear Poincaré method, means and standard deviations between CP, SG and seizure-free HR variable parameters were compared. Our results show there was increased of sympathetic andreduction in parasympathetic modulation of HRV in time and frequency domain and non-linear analysis, which was obtained from continues ECG recordings in patients during ictal phase of both epileptic groups. This altered autonomic control of HR might be responsible for increased sudden death in patients with epilepsy.

The present study showed that, as a rule, the lower the overall HRV, the lower the LF/HF ratio, and the higher positive correlation between the two parameters. This finding contradicts the traditional interpretation of LF/HF ratio as a representative of sympatho-vagal balance, not only in patients with seriously decreased HRV, whose sympathetic tone perhaps suppresses its modulation activity, but in those with quietly or even mildly decreased HRV as well. Increase of LF/HF ratio could be interpreted as an indirect evidence of the shift of sympatho-vagal balance toward predominant sympathetic modulator activityand the reduction of time domain parameters clearly indicated a diminished vagal activity and sympathetic predominance.

The present results suggest that SG seizures are mostly related to progressive diminution of cardiac vagal outflow in comparison to CP seizures. The results show different levels of increased LF, LF/HF, SD2 and SD2/SD1 ratio in the CP and SG group which suggests a mainly increased sympathetic tone, or decreased vagal tone. This apparent difference between CP and SG may be due to the different nature of the two classes of seizures, but may also relate to differences in antiepileptic drug therapy.As some researchers report ictalbradycardia in complex partial seizures [47] and as well there is some evidence, which showed that secondary generalized seizures are a major risk factor for SUDEP [16, 46] then it may give us a considerable insight into the mechanisms of ANS dysfunction and difference rates of HR variability in CP and SG seizures.

The present study agrees well with the previous studies in that epileptic seizure affects autonomic cardiac regulation and suggests that the degree of dysfunction may be related to the type of epileptic seizure. However, this study also shows that in addition to having an overall suppressing effect on the ANS function, especially SG seizures seem to be associated with increased reactivity of the cardiovascular ANS system in comparison with CP seizures.

The result of this article confirmed and extended the hypothesis of sympatho-vagal imbalance in epilepsy, as showed by lower HF and SD1 values when compared with seizure-free segments. In addition, there was a trend for higher LF, SD2, LF/HF and SD2/SD1 values in SGpatients in comparison with CP. As lower vagal (HF) and higher sympathetic (LF) tone are predictors of morbidity and mortality in cardiovascular samples, our findings highlight the importance of investigating autonomic function in patients with epilepsy in clinical practice.

In conclusion, frequency-domain and non-linear analysis of HRV showed that compared with CP seizures, sympathovagal balance in patients with SG seizures was accompanied by a significant increase in sympathetic regulation and an important decrease in parasympathetic regulation.

It should be noted that, although the seizure types lead to different behaviors in ANS and sympatho-vagl balance regulation, the localization and lateralization of seizures may playan important role in levels of these regulations. In this study, we did not investigate the localization of epileptic seizures focus in the central nervous system. Therefore, we could not have any suggestions about the different localizations and etiological reasons of the CP and SG seizures. That is why new studies must be done to define the effects of localization on the HRV parameters.

However, further studies that examine more seizure types individually will be needed to clarify the mechanism of autonomic regulation in the epileptic seizures. These studies can lead us to design the algorithms of detection and even prediction of epileptic seizures based on the information extracted from HRV signal. We are going to study more patients with CP and SG seizures in the future.

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