International Journal on Emerging Technologies 11(2): 905-909(2020)

ISSN No. (Print): 0975-8364
ISSN No. (Online): 2249-3255

After Effects of Epileptic Seizure on the Functioning of Autonomic Nervous System

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(Received 04 January 2020, Revised 03 March 2020, Accepted 05 March 2020)
(Published by Research Trend, Website: www.researchtrend.net)

ABSTRACT: Epileptic seizure is one of the most common neurological disorders in India, which can even lead to unexpected deaths. Its prediction and severity is deeply studied recently with varied approaches of heart rate variability (HRV) analyses. In this paper, a time-frequency domain investigation is presented on the post-ictal HRV signal to analyze its impact on the functioning of autonomic nervous system (ANS). Due to sudden electrical discharges during inter-ictal period, the ANS gets enormously affected which can persists for few minutes to hours. These changes are captured using statistical time domain as well as auto-regressive model based spectral parameters. To carry out the experiments, I have used PhysioNet datasets for heart rate oscillations of subjects under post-ictal state and normal subjects. Finally, Mann-Whitney U test is conducted to find the parameters which can significantly differentiate the epileptic subjects from normal subjects. It is observed from this study that the standard deviation of normal to normal (NN) intervals, median absolute deviation, and low frequency power measurements are effectual in characterizing the changes in ANS.

Keywords: Epileptic Seizure, Autonomic Nervous System, Heart Rate Variability, Auto-Regressive Spectral Analysis.

Abbreviations: ANS, autonomic nervous system; HRV, heart rate variability; SNS, sympathetic nervous system; PNS, parasympathetic nervous system; HR, heart rate; LF, low frequency; HF, high frequency; RSA, respiratory sinus arrhythmia; SVM, support vector machine; SDNN, standard deviation of normal to normal (NN) intervals: RMSSD, root mean squared differences of NN intervals; pNN50, percentage of NN intervals whose differences exceeds 50 msec; AR, auto- regression.

I. INTRODUCTION

Epileptic seizure is a type of neurological disorder which causes a short lived disturbance in the motor and sensory neurons due to abnormally higher rate of discharges of the electrical nerve impulses. In India, there are around 1.2 crores of people with epilepsy, which stresses the necessity of proper diagnosis and treatment [1, 2]. Further, it is found from literature that the cases are comparatively prevalent in children and young adults from rural areas than that from urban areas. The reason behind it may be the lesser awareness of the disease, lack of good public health infrastructures, reluctance of people to attend hospitals, social stigma, and superstitions and so on. Conversely, people from urban areas are comparatively more resolute towards healthcare. Since the root causes of epilepsy are identified to be head injury, lack of oxygen and nutrition during birth, brain tumors, encephalitis, etc., its early diagnosis is pivotal to abate its impact. Moreover, anti-epileptic drugs, proper diets and epileptic surgery are amongst the solutions to this chronic epidemic. In this context, a noninvasive and reliable diagnosis can be very helpful. Epilepsy is found to impair the functioning of autonomic nervous system (ANS) up to a few minutes or more in the post-ictal state [3-6]. The activity of ANS is widely studied using heart rate variability (HRV) analysis. In the post-ictal phase, the activity of sympathetic nervous system (SNS) is more dominating as compared to the parasympathetic nervous system (PNS). These two nervous systems are the sub-branches of ANS. Stimulation of SNS increases the heart rate (HR) and stimulation of PNS decreases HR [7]. The resultant variation in HR during the post-ictal state have a characteristic pattern which separates the epileptic HRV from normal subject's HRV. Spectral analysis of HRV signal demonstrates the presence of prominent spectral contents in three bands, known as very low frequency band (0.0033-0.04 Hz), low frequency band (0.04-0.15 Hz) , and high frequency band (0.15-0.40 Hz). The low frequency (LF) spectral power is the marker of SNS activity due to baroreflex sensitivity, while high frequency (HF) spectral content signifies PNS activity due to respiratory sinus arrhythmia (RSA) [7]. The dominance of the sub-branch can be assessed by the sympathovagal balance (LF/HF ratio), which decreases when the PNS is dominating and increases when SNS is dominating. So, it clearly signifies the health of the ANS. However, the physiological significance of very low frequency power is ignored by scientific community due to lack of adequate evidence. Dutsch *et al*., (2006) observed that temporal lobe epilepsy causes dysfunction of baroreflex sensitivity [4]. Cooman *et al*., (2018) observed an increase in ictal HR, causing tachycardia and also bradycardia at seldom. They used patient specific algorithm, which extracts information based on HR data to classify the ictal cases. They achieved 77.6% sensitivity with their approach in detecting seizure with a 57% reduction in false alarm in comparison with the patient independent technique of similar sensitivity [8]. Mungen *et al.,* (2010) performed an analysis on subjects with non-epileptic psychogenic seizures and epileptic seizure to examine its effect on ANS. They determined the R-R (one R peak of QRS waveform to the next) interval variation, sympathetic skin response and observed that there were significant difference in those parameters between the non-epileptic psychogenic seizures and epileptic seizure subjects [3]. In another study, Nilsen *et al.,* (2010) have observed significant increase in the HR in patients with secondarily generalized seizures as compared to that with complex partial seizures during pre-ictal state [9]. HR increased further during and after generalized seizures as compared to that of the subjects with partial seizures. Shamim *et al*., (2016) conducted a time-frequency domain analysis to classify the seizure and non-seizure conditions [10]. They computed temporal parameters, activity, mobility, complexity as well as spectral parameters, the mean absolute deviation of fast Fourier transform (FFT) coefficients and spectral entropy for the two conditions. The linear support vector machine (SVM) is used for their classification work, which yielded 94.2% accuracy in classifying the seizure events. Zavar *et al*., (2011) proposed an automatic seizure detection scheme using wavelet based SVM model. They extracted Lyapunov exponent, fractal dimension, and wavelet entropy from the signal to train the SVM classifier which provided 96.29% sensitivity and 100% specificity in detecting partial epilepsy [11]. Toth *et al.,* (2010) calculated time parameters, such as, mean HR, standard deviation of normal to normal (NN) intervals (SDNN), root mean squared differences of NN intervals (RMSSD) to study the variations in pre-ictal, early post-ictal and late post-ictal states. They also calculated the spectral powers for the same three phases. They found from their analysis that mean HR increases immediately after seizure, while the other time domain HRV parameters are decreased in the early post-ictal phase. The LF power was found to be decreasing in the early post-ictal phase whereas in the late post-ictal phase, the HF power had decreased [12]. Amarnath *et al*., (2110) found that power spectral density of subjects in the post-ictal state had a significantly different spectral distribution as compared to that of normal subjects [5]. Varon *et al*., (2014) have used a phase rectified signal averaging technique to detect focal and generalized seizures. They applied kernel spectral clustering algorithm to classify these two types of seizure beats from normal beats. They achieved a positive predictive value (PPV) of 86.21% and 100% sensitivity for focal seizures, and a PPV of 84.3% with 93.1% sensitivity for generalized seizures. However, it has been observed that a 100% accurate classification of seizure events are still difficult to achieve [6].

In this proposed scheme, the main aim is to find the parameters which can distinctly characterize the after effects of seizure on the ANS using HRV information and to provide a fast and accurate method for distinguishing the post-ictal HRV from normal HRV.

The remainder of the paper is organized as follows. Section II provides the details of the acquired data and the methodology pursued, Section III presents the results of the work and its discussion. Finally, Section IV concludes the paper.

II. MATERIALS AND METHODS

A. Data

Study Group: The post-ictal heart rate oscillations data are retrieved from PhysioNet data bank [13] taken from a mixed group of patients with partial epilepsy. The pattern in the data was marked by Goldberger *et al*., (2000) for the appearance of transient LF heart rate oscillations (0.01-0.1 Hz) immediately following five of 11 seizures recorded in five patients [13].

Control Group: These data are retrieved from the MIT-BIH normal sinus rhythm database containing the ECG recordings of normal subjects. It includes 18 (5 men, aged in the range of 26-45 years, and 13 women, with age in the range of 20-50 years) long-term ECG recordings [13]. The subjects were found to have no significant arrhythmias.

B. Methodology

The study to find the differences between post-ictal HR oscillations and normal HR oscillations, is initiated with the detection of outliers in the retrieved data. A few missed heart beats are observed in the data, which is found to be within acceptable limit (<1%). These data are transformed into a format containing the instances of QRS peaks and other variable contains the interbeat intervals (NN intervals).

Time domain analysis. This paper evaluates the variations in the heart rate due to seizure attacks by taking 9 minutes of post-ictal HRV data. This length of data is chosen since the proper short term HRV analysis needs at least 5 minutes of data [7] and on the other side, to capture its maximum effects on the ANS. During this period, patients normally have reduced cognitive ability, lower consciousness accompanied by muscle convulsions. This happens since the bursts of nerve impulses during the seizure attack impairs the functioning of ANS which may continue for few minutes to several hours. The functioning of ANS can be best evaluated from the HRV and sympathovagal balance [7].

To this end, the time-domain statistical parameters, namely, SDNN, RMSSD, percentage of *NN* intervals exceeding 50 msec (*pNN50*), median absolute deviation (MAD) of *NN* intervals are computed as HRV index. Mathematical expressions of these parameters are given below [7]:

$$SDNN = \sqrt{\left(\frac{1}{N}\sum_{i=1}^{N}(NN(i) - \overline{NN})^2\right)} \quad (1)$$

where *N* is the total number of *NN* intervals, $NN(i)$ is the i^{th} *NN* interval, and $\overline{NN}$ is the average of the *NN* intervals.

$$RMSSD = \frac{1}{N-1}\sqrt{\sum_{i=1}^{N-1}[NN(i+1) - NN(i)]^2} \quad (2)$$

NN50 =Total number of consecutive *NN* intervals whose differences is more than 50 ms.

$$pNN50 = \frac{\mathrm{NN50}}{\text{Total number of NN intervals}} \times 100\% \quad (3)$$

$$MAD = \mathrm{median}[NN(i) - \overline{NN}] \quad (4)$$

Spectral Analysis using Auto-Regression (AR) method. The power spectral density of *NN* intervals are obtained by using the AR modelling of the series formed by the NN intervals. As per AR model, the output of a time series can be given by [14].

$$y(n) = -\sum_{i=1}^{q} a_i\, y(n-i) + Gx(n) \quad (5)$$

where *y(n)* is the output, a_i is the i^{th} coefficient, q is the order of the model, G is the gain factor, and x(n) is the white noise.

Since this model contains only poles, it is also known by all poles model [14]. The power spectral density (PSD) of a time series can be obtained by various techniques; however in this paper, the covariance method is used. The main idea in this method is to minimize the prediction error power, which can be given by the following equations:

$$\varepsilon = -\frac{1}{N-q}\sum_{n=q}^{N-1}|a_i y(n-i) + Gx(n)|^2 \quad (6)$$

$$P(f) = \frac{\hat{\sigma}^2}{\left|1+\sum_{i=1}^{p}\widehat{a_i}.e^{-i2\pi fk}\right|^2} \quad (7)$$

where $P(f)$ is the estimated power for frequency f, $\hat{\sigma}^2$ is the noise variance, and $\hat{a}_i$ is the estimated AR coefficient. From the estimated PSD, the LF power, HF power and LF/HF ratio are obtained to evaluate the shift of the sympathovagal balance.

Statistical Significance Test. The distribution of the data are unknown and sample size are different in the experimental and control group of this study. Besides, the samples are independent and different, which led to choose a non-parametric significance test suitable for unmatched data. In this context, Mann-Whitney U test is selected for studying the two sets of data. As per this test, if the *p*- value for two variables is found to be lesser than 0.05, then there is significant difference between the two variables. The further details about Mann-Whitney U-test can be obtained in [15].

III. RESULTS AND DISCUSSION

To carry out the time and spectral analysis, I have used 9 minutes of post-ictal HRV data of 7 partially epileptic subjects and 11 normal subjects, all collected from PhysioNet databank as briefed in Materials and Method section. The findings of the both types of approaches for partially epileptic subjects are shown in Table 1. Again, the same for normal subjects are shown in Table 2. The result shows that specifically SDNN, MAD, and LF power are much lower in case of the epileptic subjects after the seizure events. This indicates the dysfunction of SNS, which increases the HR and its variability in a drastic manner. This effect on ANS is probably responsible for the generally observed overshoot of Blood Pressure (BP), convulsions and lower cognitive ability in such patients after the seizure attacks. To validate the result of time domain analysis, spectral analysis is also conducted using PSD (based on AR method), whose results are shown in Fig. 1. It can be observed from the figure that LF power has dropped in the post-ictal phase as compared that of normal subjects; whereas HF power has increased in case of post-ictal phase. It indicates normal PNS activity. However, the impaired SNS is sufficient to cause the irregularity. The sustained oscillations of the SNS can cause long-term damage or even death. It has also been observed the trend for RMSSD and *pNN50* changes varies substantially within the post-ictal phase of different subjects. This suggests the unsuitability of these two parameters to capture the changes occurred to ANS for such cases of seizure events.

From Table 3, it can be inferred that the parameters SDNN, MAD and LF power can significantly differentiate the post-ictal subjects from the normal subjects as the p value is found to be much lesser than 0.05. Similarly higher ranks are given for this parameters.

Table 1: HRV parameters for partially epileptic patients in post-ictal phase.

Parameters	SZ 01	SZ 02	SZ 03	SZ 04	SZ 05	SZ 06	SZ 07
SDNN (ms)	66.89	45.87	60.58	49.26	36.63	46.82	39.22
RMSSD (ms)	26.27	49.07	26.85	41.67	13.23	26.77	17.02
pNN50	3.78	13.78	3.44	11.01	0.33	3.11	0.44
MAD (ms)	25.1	34.9	32.1	32.1	16.22	29.8	17.5
LF power	0.20	0.34	0.48	0.43	0.11	0.15	0.12
HF power	0.22	0.89	0.23	0.67	0.04	0.14	0.07
LF/HF ratio	0.91	0.39	2.13	0.64	2.17	1.11	1.83

Table 2: HRV parameters for Normal subjects.

Parameters	Normal 1	Normal 2	Normal 3	Normal 4	Normal 5	Normal 6	Normal 7	Normal 8	Normal 9	Normal 10	Normal 11
SDNN (ms)	112.46	104.57	75.26	38.67	93.06	123.86	55.91	155.56	100.51	90.09	59.68
RMSSD (ms)	0.03	0.03	0.03	0.02	0.06	0.04	0.03	0.05	0.02	0.04	0.03
pNN50	3.77	4.33	6.55	2.78	9.00	10.33	7.00	13.34	3.22	12.00	7.89
MAD (ms)	62.1	71.21	55.1	36.4	55.2	85.9	32.1	116.8	70.1	55	31.4
LF power	0.66	0.98	0.33	0.27	1.21	1.56	0.92	1.33	0.40	1.07	0.65
HF power	0.34	0.23	0.15	0.05	1.12	0.66	0.46	0.71	0.14	0.62	0.43
LF/HF ratio	1.94	4.23	2.13	5.00	1.16	2.36	1.98	1.87	2.83	1.73	1.53

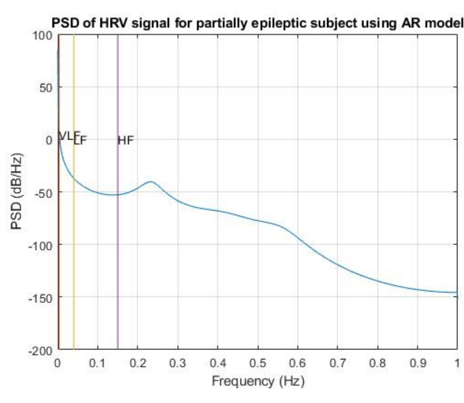

Fig. 1. PSD of HRV signal (NN intervals) during post-ictal phase.

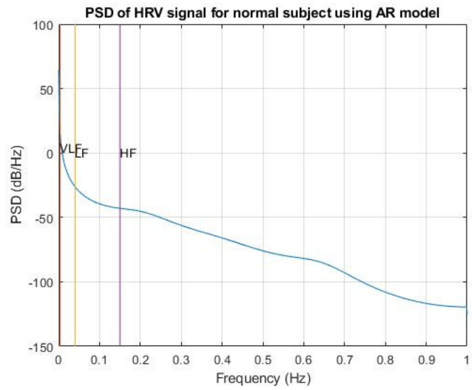

Fig. 2. PSD of HRV signal (NN intervals) formal normal subjects.

Table 3: Mann Whitney U-test.

Features	Epileptic Seizure (mean±SD)	Normal Subjects (mean+SD)	Mann Whitney U value	*p*-value
SDNN (ms)	49.32±10.92	91.78±33.43	10	0.008*
RMSSD (ms)	28.7±12.73	34.44±11.24	24	0.211
pNN50	5.13±4.83	7.29±3.60	26	0.258
MAD (ms)	26.06±7.34	61.09±25.11	7	0.003*
LF power	0.26±0.15	0.85±0.42	8	0.004*
HF power	0.32±0.30	0.45±0.31	36	0.626
LF/HF ratio	1.31±0.72	2.13±1.47	16	0.044*

This hints that the ANS functioning for post-ictal phase can be successfully assessed using these parameters. Besides, the possibility of using these parameters to predict the upcoming seizure events in such patients can be experimented.

IV. CONCLUSION

This paper presents a computationally simple method to identify the characteristics of post-ictal HRV data. Moreover, the effects of seizure events on the functionality of ANS is also studied, which leads to elevated BP, convulsions and cognitive impairments. It is found from Mann Whitney U-test that some of the HRV indices such as, SDNN, MAD, and LF power are significantly lower as compared to that of normal subjects. These show depressed SNS activity during the post-ictal phase, which can cause harm to heart and brain notably. The intra group variations are also observed in post-ictal HRV of subjects, whose pre-ictal information could have provided more clear idea about seizure onsets as well as its prediction.

V. FUTURE SCOPE

This work can be extended to develop automatic classifier for separating peri-ictal subjects with normal subjects using machine learning algorithms. The EEG data with pre-, inter- and post-ictal data can be utilized to provide prior alert to subjects.

Conflict of Interest. I confirm that there is no known conflicts of interest associated with this work.

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How to cite this article: Deka, D. (2020). After Effects of Epileptic Seizure on the Functioning of Autonomic Nervous System. *International Journal on Emerging Technologies*, *11*(2): 905-–909.