Neurology Asia 2022; 27(3) : 649 – 661

Retrospective analysis of autonomic dysfunction in epilepsy patients from neurophysiological recordings

[3]Akash Rahul Shridharani, [1,2,5]Harilal Parasuram, [3]Mrudula Balaraman, [4]Renjitha Bhaskaran, [2,5]Anand Kumar, [1,2,5]Siby Gopinath

[1]Amrita Advanced Centre for Epilepsy (AACE), Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi, Kerala; [2]Department of Neurology, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi, Kerala; [3]School of Engineering, Amrita Vishwa Vidyapeetham, Ettimadai, Coimbatore; [4]Department of Biostatistics, Amrita School of Medicine, Amrita Vishwa Vidyapeetham, Kochi, Kerala; [5]Amrita Mind Brain Center, Amrita Vishwa Vidyapeetham, Amritapuri Campus, Kollam, Kerala, India.

Abstract

Autonomic dysfunction is often associated with seizures in patients with epilepsy. Autonomic dysfunction during seizures can cause serious events like cardiac arrest and sudden unexplained death. Early detection of autonomic dysfunction is crucial to avoid such medical emergencies. In our study, we analyzed the heart rate variability (HRV) in physiological recording during the preictal, ictal and postictal periods. A total of 142 seizures with various semiologies recorded from 49 epilepsy patients were included. Time-domain measurements including mean hear rate (HR), RR interval (RRI), root-mean-square of successive R-R interval differences (RMSSD), The standard deviation of N-N intervals (SDNN) and percentage of successive RR intervals that differ by more than 50 ms(pNN50) were analyzed at different time points, 20 minutes before the seizure, 1 minute before the seizure, during the seizure and 20 minutes after the seizure. We observed there was a significant difference in HRV parameters during and just before the seizure onset (RMSSD with p-value<0.001 and SDNN with p-value<0.001). We also observed that there was a suppression of parasympathetic activity and activation of sympathetic stimulation in the ictal and peri-ictal period, which was characterized by an elevation in the mean heart rate (HR), whereas the mean RRI showed an inversely proportional trend. There was a reduction in mean RMSSD, SDNN and pNN50 prior to seizure onset and was more pronounced in generalized seizures as compared to focal seizures with preserved or impaired awareness. There was a greater sympathetic activation and parasympathetic inhibition during an epileptic seizure in females as compared to male patients. These findings suggest that autonomic dysregulation was increased during a generalized seizure when compared to a focal seizure. HRV analysis can be used as a valid method for quantifying central influences on the autonomic nervous system and its cardiac control. A major advantage of electrocardiogram (ECG)-based seizure detection is that the ECG is an essentially easier signal to obtain, with a higher signal-to-noise ratio than EEG (electroencephalogram). Based on the inferences from this study future studies could be done to build machine learning models which could form the base for the development of wearable seizure prediction devices.

Keywords: Heart rate variability, epilepsy, autonomic dysregulation, EEG, RMSSD.

INTRODUCTION

Epilepsy is a chronic neurological disorder that significantly affects the patient's quality of life. It is the 2nd most common neurological disorder, after stroke, affecting, on an average 50 million people worldwide.[1] The International League Against Epilepsy (ILAE) proposed that epilepsy be considered to be a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 hours apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the

Address correspondence to: Dr. Siby Gopinath, DNB (Neurology), Amrita Advanced Centre for Epilepsy, Amrita Institute of Medical Science, Amrita Vishwa Vidyapeetham University, Kochi, India. Email: sibygopinath@aims.amrita.edu

Date of Submission: 2 December 2021; Date of Acceptance: 13 April 2022

https://doi.org/10.54029/2022mpp

general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome.[2]

Pathophysiologically, epileptic seizures occur due to abnormal hypersynchronization from cortical neuronal networks because of abnormal bursts of electrical activity from the brain. It is the unpredictability and suddenness of the seizures that make them so dangerous. Not only does a seizure cause metabolic changes at a cellular level leading to damage to these neuronal networks but it also carries a small risk due to the autonomic dysfunction associated with it. The most feared complication related to autonomic dysfunction is the involvement of the cardiac and respiratory systems. A particular complication related to epilepsy is Sudden Unexpected Death in Epilepsy (SUDEP).

The somatic, emotional and autonomic networks of the brain can be monitored through various modalities. Many of the manifestations of a seizure are due to autonomic dysfunction, such as perspiration, frothing from the mouth, a rising sensation in the abdomen, tachycardia, elevated BP and bowel/bladder incontinence. Most of the time, our monitoring techniques neglect the autonomic networks. An ECG recording is relatively easy to perform and interpret. ECG-based algorithms are certainly more practical and convenient than devices using EEG signals. The high signal-to-noise ratio and ease of recording favour ECG over EEG-based approaches. In addition, as about 82% of epileptic seizures are associated with ictal tachycardia (which often precede ictal EEG changes)[3], the proposed method of seizure detection/prediction based on Heart Rate Variability (HRV) parameters may be very useful for seizure warning devices.[4]

Studies have reported that linear and non-linear parameters of HRV may reflect sympathetic and parasympathetic nervous system activity.[5] HRV analyses were based on the measurement of the time intervals between successive QRS complexes, which represents the regulation of the HR by the autonomic nervous system via its sympathetic and parasympathetic control mechanisms. Hence, HRV analysis can be used as a measure for the assessment of autonomic nervous system activity. The study by Malarvili et al. has reported a sensitivity of 85.7% and a specificity of 84.6% in the prediction of seizure from ECG.[6]

This means that we can utilize the ECG signals recorded during epilepsy monitoring to detect or predict seizures. HRV can be considered an indicator of sympathetic and parasympathetic dysfunction associated with epileptic seizures. The degree of autonomic dysfunction can vary in different types of seizures.[7] Therefore, a detailed analysis of HRV properties is crucial to understanding the association of autonomic dysfunction in various types of epilepsy. However, there may be many confounding factors that may affect HRV parameters such as concomitant cardiac diseases, drugs, duration of epilepsy, and ongoing AEDs.

In this study, we analyzed the HRV parameters to study autonomic dysfunction in epilepsy patients with various seizure types. The main objectives of our study were to study 1) the autonomic dysfunction in epilepsy patients at different time intervals including pre-ictal, ictal and post-ictal, 2) HRV parameters in different types of seizures, 3) gender variation in HR parameters and 4) its relation to the side of onset of the seizures.

METHODS

Selection of study participants

Data used for this retrospective, single-centre, blinded observational study was acquired between January 2019 to January 2020. Patients admitted to our Epilepsy Monitoring Unit for prolonged Video EEG monitoring who had one or more seizures during the recording were included in this study. The patient who had pre-existing cardiac comorbidities, patients with age < 1 year or > 80 years and the neurophysiological recording contaminated by various artifacts were excluded from the study. We shortlisted data from 49 epilepsy patients for the analysis after applying the inclusion and exclusion criteria. Among 49 patients, the epileptologist included 142 seizures that met the inclusion criteria. The study was approved by the Scientific Research and Clinical (Ethics) Committee.

Data used for this retrospective, single-centre, blinded observational study was acquired between January 2019 to January 2020. Patients admitted to our Epilepsy Monitoring Unit for prolonged Video EEG monitoring who had one or more seizures during the recording were included in this study. The patient who had pre-existing cardiac comorbidities, patients with age < 1 year or > 80 years and the neurophysiological recording contaminated by various artifacts were excluded from the study. We shortlisted data from 49 epilepsy patients for the analysis after applying the inclusion and exclusion criteria. Among 49

patients, the epileptologist included 142 seizures which that met the inclusion criteria. The study was approved by the Scientific Research and Clinical (Ethics) Committee.

Data preprocessing

The ECG and EEG were acquired using Nicolet One EEG machines and NatusNeuroworks 7.1.0 software. Pre-ictal, ictal and post-ictal EEGs were selected for analysis (see Figure 1). All machines were calibrated before each patient recording. Electroclinical and electrographic seizures were identified based on video monitoring and response checking during a suspected event and then correlated with the EEG. The EEG ictal onset was used as the reference point for HRV analysis. Signal processing and HRV feature extraction was performed using a computer program implemented in MATLAB.

ECG and respiratory signals are prone to be affected by various artifacts including baseline wander, power line noise, and electromyographic noise. Baseline wander is a low-frequency noise in the frequency band from 0.5 to 0.6 Hz that occurred due to the movement of electrodes during the patient's movements or breathing.[8] Power line interference was caused by electrical appliances and may introduce 50 Hz frequency noises in the signal. All these noises can lead to a wrong interpretation of physiological signals and functions. In our study, digital filters were used to remove artifacts from the recordings, a notch filter at 50 Hz was used to remove the power line interferences and a kaiser window coefficient and finite impulse response filter were used to eliminate the baseline drift.[9]

The R-R intervals were extracted from the ECG signal for further extraction of the Heart rate variability features such as heart rate (bpm), Inter beat interval (ms), and PNN50 (%). (see Table 1)

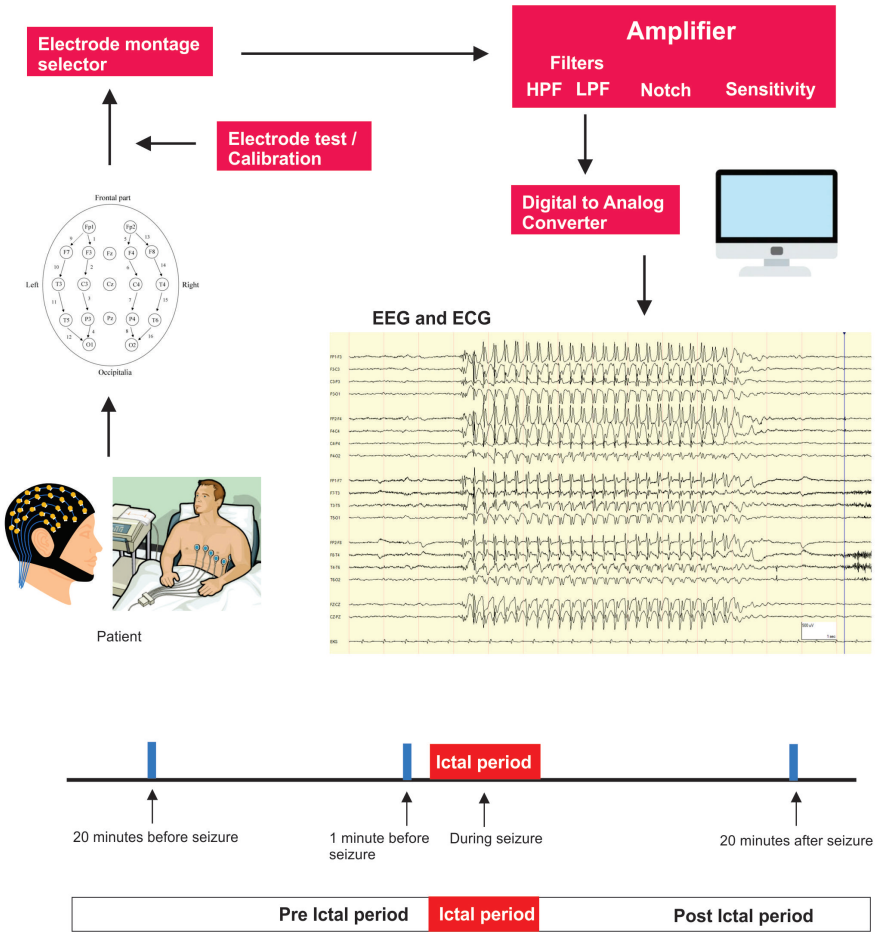

Figure 1. Neurophysiology signal acquisition. A. Components of EEG machine B. Intervals marked for computation of HRV measurements.

Table 1: HRV parameters estimated for ECG signal

No	Parameter	Equation	Estimated value	Reported Range
1	**SDNN (ms)** The standard deviation of N-N intervals	$\sigma = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(x_i - \mu)^2}$ N denotes total time, X denotes features and μ denotes mean.	55	32–93
2	**BPM** The average number of beats in a minute	$BPM = \frac{\Sigma \ R\text{-}peaks}{duration\ in\ minutes}$ R-peaks denotes total number of successive R-peaks values	64	60-100
3	**RR interval Avg** Difference between peak to peak interval by the total number of peaks	$duration(sec) = \frac{\Sigma \ R\text{-}peaks}{sampling\ rate}$	936	785–1,160
4	**RMSSD(ms)** Root-mean-square of successive R-R interval differences	$= \frac{\Sigma_{i=1}^{n} \ R\text{-}peaks_{i+1} - R - pea}{n}$	44	19–75
5	**pNN50 (%)** Percentage of successive RR intervals that differ by more than 50 ms	Percentage of successive RR intervals that differ by more than 50 ms	15	3-23

Time-domain measurements including mean Hear Rate (HR), RR interval (RRI), Root-mean-square of successive R-R interval differences (RMSSD), The standard deviation of N-N intervals (SDNN) and Percentage of successive RR intervals that differ by more than 50 ms(pNN50) were analyzed at different time points 20 minutes before the seizure, 1 minute before the seizure, during the seizure and 20 minutes after the seizure for all epileptic seizure were analyzed in this study. Previous studies have reported significant changes in HRV parameters 5 minutes prior to the ictal onset and some studies have demonstrated HR variations 15- 20 minutes prior to and 10 min after seizure onset.[10,11] In our study, we extracted HRV signals from 20 minutes prior to the ictal onset and 20 minutes after the seizure offset. While the conventional short-term recording standard was 5 minutes, researchers have proposed ultra- short-term recording periods from 60 to 240 seconds.[12] In our study, we used 2 minutes segments at various states for estimating the time domain parameters. HRV analysis was done during the ictal period in such a way that it did not overlap with the immediate preictal period.

Estimating autonomic dysfunction

We studied time-domain measurements of HRV at 20 minutes before the seizure in the interictal period, 1 minute before in the pre-ictal period, a period of approximately 10 seconds during the seizure (i.e. ictal period) and 20 minutes after the seizures in the post-ictal period (see Figure 1). The change in these HRV measurements denotes significant sympathetic and parasympathetic dysfunction. This in turn may be dangerous as there is a likelihood of these patients developing deadly dysrhythmias and sometimes cardiac arrest. We also compared various types of seizure semiology and see which particular type has more chances of developing fatal arrhythmias.

Statistical analysis

Paired t-test was used to test the statistical significance of the difference in the mean HRV measures at different states (interictal, preictal, ictal and postictal). The statistical significance of the percentage changes in the HRV measures for gender was tested using the Mann Whitney U test. The statistical significance of the percentage changes in the HRV measures between the type of seizures was tested using the Kruskal Wallis

Table 2: Distribution of type of events

Type of events	Number of events	Percentage
Focal seizures with preserved awareness	23	16.2
Focal seizures with impaired awareness	73	51.4
Generalized seizures	45	31.7
Psychogenic seizures	1	0.7

test and the Dun Bonferonni correction test (for multiple comparisons). The Kruskal Wallis test was also used to test the statistical significance of the HR variations amongst the sides of onset. All statistical analysis was performed using IBM SPSS version 20.0 software.

RESULTS

Demographics

The mean age of patients included in the study was 27.14 ± 12.15 years with a minimum age of 5 years and maximum age of 58 years. Twenty-four (49%) were males and 25 (51%) were females. Out of 142 seizures studied, 23 were focal seizures with preserved awareness, 73 were focal seizures with impaired awareness, 45 were generalized seizures and 1 patient had psychogenic seizures (see Table 2). Amongst the 49 patients, we observed that generalized seizures were more common in the younger population and as the age progressed the incidence of focal seizures increased (see Table 2 and Figure 2). Out of 142 seizures studied, 67 were of temporal onset and 75 extra-temporal. Similarly, out of 142 events, 29 were of right hemispheric onset, 31 left-hemispheric and the rest were bilateral.

HRV parameters predicted epileptic seizure and autonomic dysfunction

We compared the mean HR, RRI, RMSSD, SDNN and pNN50 20 minutes before the seizure to during the seizure to 20 minutes after the seizures (see Figure 3). The analysis showed statistically significant differences in the estimated HRV parameters during and just before the seizure onset for RMSSD with p-value<0.001 and SDNN with p-value<0.001 (see Table 3). We also observed there was a suppression of parasympathetic activity and activation of sympathetic stimulation in the ictal and peri-ictal period, which was characterized by an elevation in the mean heart rate (HR), whereas the mean RRI showed an inversely proportional trend (see Table 3).

We also found that out of 142 seizures, 44 episodes were associated with ictal or peri-ictal autonomic dysfunction as demonstrated by significant bradycardia or tachycardia while approaching the ictal period. The heart rate was compared between 20 minutes before the seizure

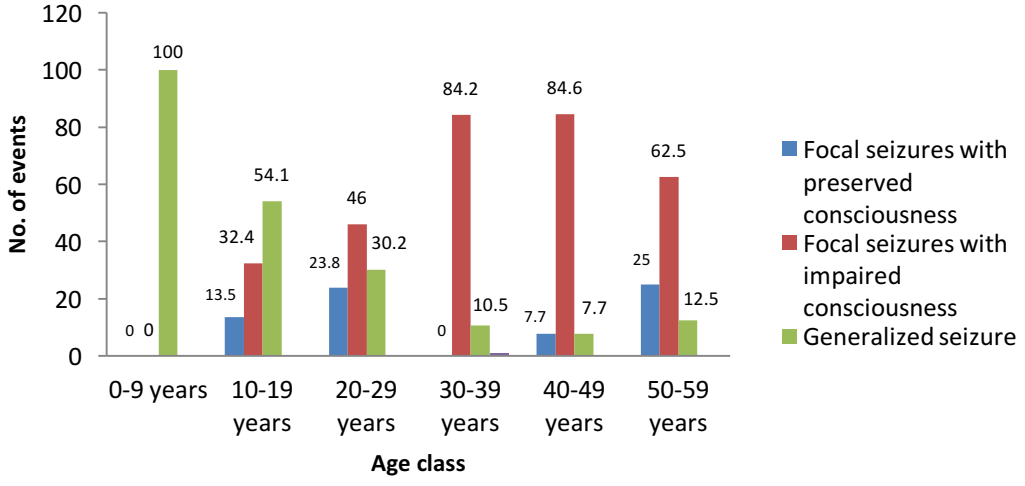

Figure 2. Distribution of various types of seizures in different age groups

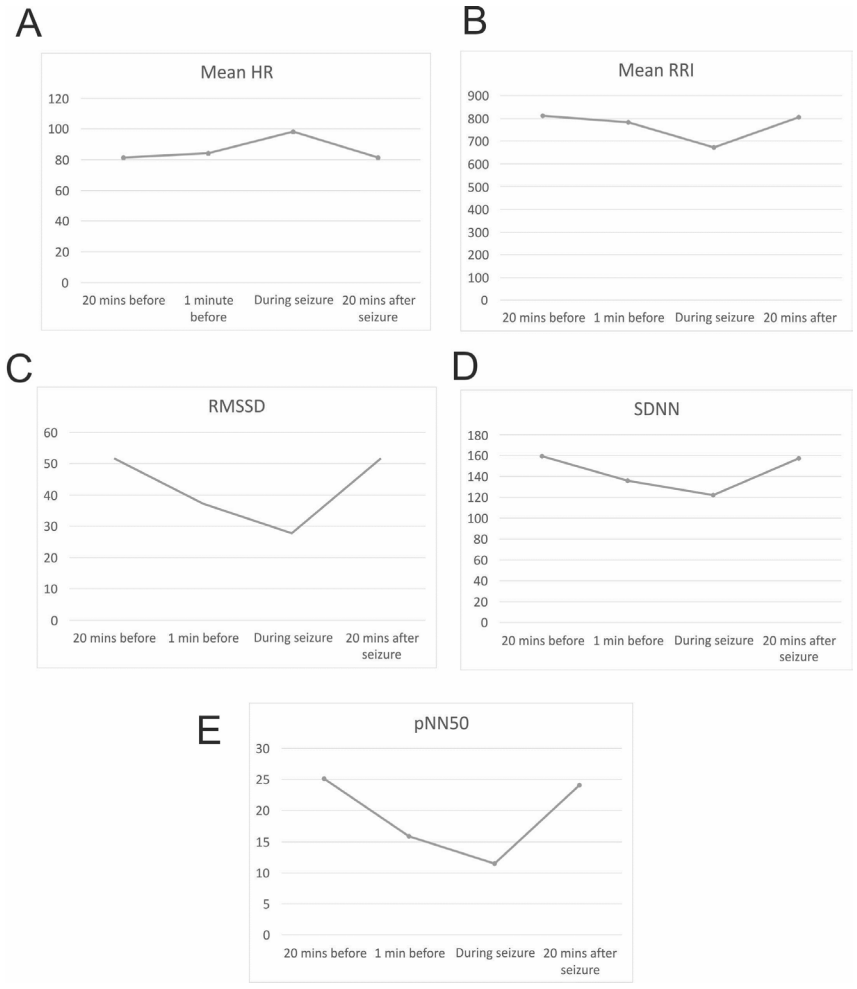

Figure 3. Line diagram showing the trend of mean HRV parameters at various time intervals. mean HR (A), mean RRI (B), mean RMSSD (C), mean SDNN (D) and mean pNN50 (E)

and 1 minute before or during the seizure. If there was a heart rate change of +/_ 10 beats per minute, as compared to baseline, then it was considered a significant autonomic dysfunction.

Multiple comparisons

Multiple pair comparison of percentage changes in mean RMSSD, SDNN and pNN50 at different time intervals was performed. In the analysis, type 1 is Focal seizures with preserved awareness, type 2 is Focal seizures with impaired awareness, and type 3 is Generalized seizures.

For percentage change between 20 mins before to 1 mins before seizure onset, a statistical significant difference was observed for pNN50, in type 1-3 (p-value = 0.026) and type 2-3 (pvalue = 0.005); for RMSSD, in type 1-3(p-value< 0.001) and type 1-2 (pvalue < 0.001); for SDNN, all pairs were found to be statistically significant (see table 4).

For percentage change between 20 min before to during the seizure, a statistical significant difference was observed for pNN50, in type 1-3 (p value = 0.053, borderline) and type 2-3 (p-value = 0.008); for RMSSD, in type 1-3 (p-value< 0.001) and type 1-2 (pvalue < 0.001); for SDNN, all pairs were found to be statistically significant (see Table 4).

For percentage change between 1min before and during a seizure, a statistically significant difference was observed for RMSSD, in type 1-2 (p-value = 0.005); and for SDNN, all pairs were found to be statistically significant (see Table 4).

For percentage change between during seizure and 20 min after the seizure, a statistical significant difference was observed for pNN50, in type 2 -3 (p value < 0.001); for RMSSD, in type 1-3

Table 3: Percentage change in mean RMSSD, SDNN and pNN50 at different time intervals with respect to type of seizures. In the table, type 1 is Focal seizures with preserved awareness, type 2 is Focal seizures with impaired awareness, type 3 is Generalized seizures

	Type of Events	n	Percentage of successive RR intervals that differ by more than 50 ms(pNN50)		p-value	Root-mean-square of successive R-R interval differences (RMSSD)		p-value	The standard deviation of N-N intervals (SDNN)		p-value
			Mean±SD	Median (IQR)		Mean±SD	Median (IQR)		Mean±SD	Median (IQR)	
20 mins before to 1 min before	1	23	23.57±46.7	30.7 (13.6-50)	0.003	13.34±26.5	15.8 (12.2-22)	<0.001	4.63±2.8	4.3 (2.6-6.3)	<0.001
	2	73	34.13±21.52	30 (19.2-45.7)		28.77±21.4	30.6 (21.4-36.9)		12.14±6.5	11.8 (7.4-15.3)	
	3	45	45.35±19.41	41.4 (32.7-56.3)		33.21±21.3	33.2 (18.3-51.6)		23.13±9.3	24.1 (16-29.6)	
20 mins before to during seizure	1	23	42.69±49.85	58.3 (20-72)	0.006	30.05±31.4	23.4 (17-31.5)	<0.001	6.84±3.3	7.3 (4.2-9.8)	<0.001
	2	73	51.99±24.73	50 (28-67)		47.24±17.5	46 (38.3-58)		19.12±7.9	17 (13.9-22.5)	
	3	45	65.22±18.13	67.7 (55-75)		50.58±18.4	49.7 (33.9-65.0)		36.64±9.9	37.7 (32.7-42.3)	
1 min before to during seizure	1	23	29.34±29.7	30 (3.7-54.5)	0.145	-2138.2±-2337.8	-2035 (-2337-1885.9)	<0.001	2.30±2.8	1.9 (0-5)	<0.001
	2	73	30.48±27.6	22.4 (11-47)		-2330.3±-2337.8	-1991 (-2897-1431)		8.01±5.8	7 (4.3-10)	
	3	45	36.36±26.26	41.7 (19.9-51.2)		-1452.1±-1648.2	-13273.8 (-1648-918)		17.40±9.5	19 (8.4-24.2)	
During seizure to 20 mins after seizure	1	23	-234.29±310.4	-110 (-340--25)	0.001	-77.95±123.0	-30.2 (-51-19.5)	<0.001	-5.70±4.00	-4.5 (-7.2-2.68)	<0.001
	2	73	-173.88±283.8	-71.8 (-163.6-32.5)		-122.62±99.6	-87 (-131.4-65)		-23.61±18.3	-19.2 (-30.5-13.7)	
	3	45	-247.56±234.31	-177 (-287.5-110.8)		-131.85±130.7	-87 (-160.8-49.8)		-59.73±24	-57.9 (-73.6-43.8)	

Table 4: Multiple pair comparison test for percentage changes in mean RMSSD, SDNN and pNN50 at different time intervals and seizure types. In the table, type 1 is Focal seizures with preserved awareness, type 2 is Focal seizures with impaired awareness, and type 3 is generalized seizures

	Type of Events pairs	Percentage of successive RR intervals that differ by more than 50 ms(pNN50)	Root-mean-square of successive R-R interval differences (RMSSD)	The standard deviation of N-N intervals (SDNN)
		p value	p value	p value
20 mins before to 1 min before	1-2	1.00	< 0.001	< 0.001
	2-3	0.005	1.00	< 0.001
	1-3	0.026	< 0.001	< 0.001
20 mins before to during seizure	1-2	1.00	<0.001	< 0.001
	2-3	0.008	1.00	< 0.001
	1-3	0.053	<0.001	< 0.001
1 min before to during seizure	1-2	-	0.005	< 0.001
	2-3	-	0.887	< 0.001
	1-3	-	0.094	< 0.001
During seizure to 20 mins after seizure	1-2	0.885	< 0.001	< 0.001
	2-3	<0.001	1.00	< 0.001
	1-3	0.172	< 0.001	< 0.001

(p-value< 0.001) and type 1-2 (pvalue < 0.001); for SDNN, all pairs were found to be statistically significant (see Table 4).

Analysis revealed a significant statistical difference in HRV parameters for focal seizures with preserved awareness and impaired awareness and generalized seizures

We compared the mean HR at 20 minutes before to 1 min before, 20 minutes before to during the seizure and during the seizure to 20 minutes after the seizure, there was a significant difference between focal seizures with impaired awareness and focal seizures with preserved awareness (p-value <0.0001). As the mean HR was inversely proportional to the mean of RR interval it also showed similar differences. Similar differences were noted when various time intervals were compared amongst each other for various HRV measurements like mean RMSSD and SDNN (see Figure 4). Thus, mean HR, RR interval, RMSSD and SDNN showed a significant difference between focal seizures with impaired awareness, focal seizures with preserved awareness and generalized seizures. Although for pNN50, the difference between focal seizures with preserved awareness and impaired awareness was not significant at time intervals - 20 minutes before to 1 min before, 20 minutes before to during the seizure, and during the seizure to 20 minutes after the seizure (p values – 1.000, 1.000 and 0.172 respectively). Also, pNN50, when compared between focal seizures with impaired awareness and generalized seizures at the time interval – during the seizure to 20 minutes after the seizure was not significant (p-value is 0.885)(see Figure 4) Thus, all HRV parameters except pNN50 vary more in patients with generalized seizures as compared to focal seizures with impaired awareness and focal seizures with preserved awareness, meaning the autonomic instability to be more in patients with generalized seizures.

Gender differences in mean HRV parameters

We observed an elevation in the mean HR and a reduction in RRI, RMSSD, SDNN and pNN50 in the immediate pre-ictal and ictal period (see figure 5). The change of mean HR (p-value<0.001), RRI (p-value = 0.001) and SDNN (p-value = 0.025) with respect to gender showed a major difference (Figure 5). The change in these parameters was much higher in females as compared to males. There was a greater sympathetic activation and

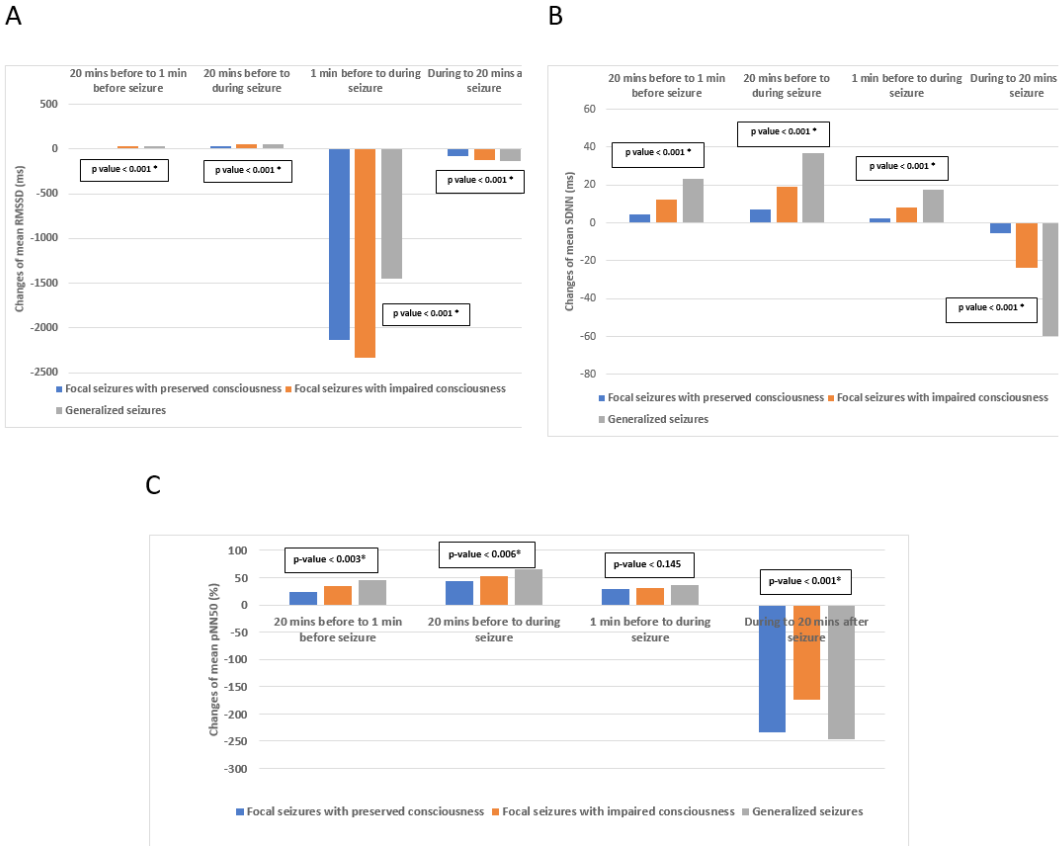

Figure 4. Statistical analysis of HRV parameters for focal seizures with preserved awareness and impaired awareness. Change in mean RMSSD (A), SDNN (B) and pNN50 (C) for all types of seizures. The asterisks ('*') in the p-value indicate the statistical significance.

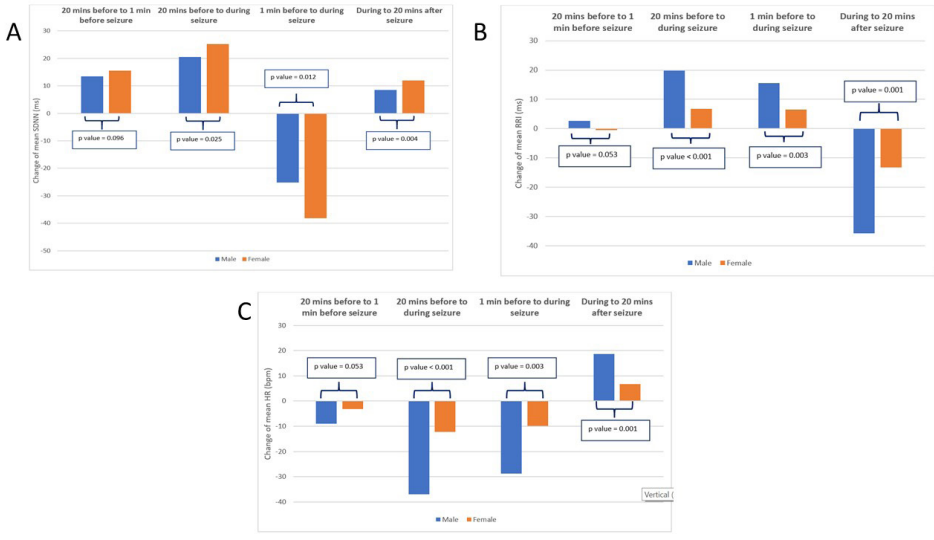

Figure 5. Gender comparison showed differences in mean HRV parameters. A – Change of mean SDNN (ms) B – Change of mean RRI (ms) C – Change of mean HR (bpm)

parasympathetic inhibition during an epileptic seizure in females as compared to males. However, comparison of percentage changes of RMSSD (p-value = 0.340) and pNN50 (p-value = 0.317) did not show any significant difference with respect to gender.

Comparison between temporal and extratemporal onset seizures

We also made a comparison between temporal and extratemporal onset seizures and found that there was a statistically significant difference when comparisons were made for RMSSD, pNN50 and SDNN. Here, the important time frames which demanded comparison were the difference between the pre-ictal state (20 minutes before the seizure) and peri-ictal or ictal state (1 minute before or during the seizure). Difference between 20 minutes before the seizure and 1 minute before the seizure for RMSSD (p-value = 0.001) and SDNN (p-value < 0.0001) was statistically significant. However, same comparison for pNN50 was not statistically significant (p-value = 0.824). Similarly, comparison was made for RMSSD (p-value < 0.0001), pNN50 (p-value = 0.014) and SDNN (p-value < 0.0001) for time frames, 20 minutes before the seizures and during the seizure and this comparison was statistically significant.

Analysis for comparison of the side of onset

We made a comparison between the sides of the onset of the seizure as well, and we took into account whether the onset was on the right side, left or both sides. We found a statistically significant difference in comparing the side of onset when we compared RMSSD (p-value = 0.003) and SDNN(p-value = 0.008), 20 minutes before the seizure to during the seizure. Furthermore, we also found that there was a statistically significant difference in RMSSD when seizures originated from the left side as compared to when the origin of seizure was from both sides. The difference was most significant when a comparison was made between RMSSD, 20 minutes before the onset of the seizure to RMSSD during the seizure. The weighted average for RMSSD, 20 minutes before the seizure onset to during the seizure onset for the left-sided onset was higher than when the onset was from the right or both sides.

DISCUSSION

Amongst the many complications associated with autonomic dysfunction during an epileptic seizure, SUDEP is the most dreaded. It is prudent to anticipate such difficulties in the management of epilepsy and take preventive measures. HRV can provide an accurate measure of autonomic dysfunction.

In our analysis, significant tachycardia was observed as the time interval approached the peri-ictal period and in the post-ictal period, it transitioned back to normal. Out of 142 seizures, 44 events had an associated tachycardia or bradycardia during the ictal or peri-ictal period, as compared to the baseline, which was 20 mins before the seizures. Ictal tachycardia or bradycardia was defined as a heart rate rise or drop of 10 beats per min from the baseline.[11] The finding was comparable to an Austrian study where tachycardia occurred in 98% of children suffering complex partial seizures of temporal lobe origin.[13] However, their study was only limited to the pediatric population and only assessed HRV parameters for complex partial seizures. A comparable trend was noted in a German study, which demonstrated peri-ictal tachycardia.[14] But here, epileptic convulsions were compared with non-epileptic events. It was concluded that, if ictal HR increased by ≥30 % from the baseline, there was a 97 % chance that this spell was epileptic. Other linear or non-linear parameters were not evaluated.

The mean RR intervals are indirectly proportional to the mean heart rate. In our study also it was found that as the time interval approached the time to seizure onset, there was a decrease in the mean RR interval which showed a statistically significant difference.

Amongst the different time intervals when compared between males and females, there was a statistically significant difference found in mean HR, SDNN and mean RRI. The change in SDNN during interictal to ictal was significantly higher in females as compared to males, suggesting that the sympathetic activation and parasympathetic inhibition in females were more. However, no significant difference was found between males and females in HRV time-domain parameters like RMSSD and pNN50. In normal patients, however, it was found that in a meta-analysis of 296,247 healthy participants, women had higher mean HR (smaller RR intervals) and lower SDNN and SDNN index values, especially in 24 h studies, compared to men.[15] However, in a study by Shaffer et al women showed relative vagal dominance, despite higher mean HR and men showed relative sympathetic nervous system dominance, despite their lower HR.[16]

We also validated the previously reported finding of the vagal tone during the seizures.[14,17-19] We observed that vagal tone was reduced during the seizure and immediately before the seizure onset. SDNN indirectly represents sympathetic and parasympathetic activity. A significant drop in SDNN measurements in the inter-ictal period has been reported in the earlier study.[20] In our study, a similar trend was observed in estimated SDNN and RMSSD during interictal to ictal transition. We also observed a significant reduction in pNN50 measurements in the immediate pre-ictal and ictal periods.

A few studies compared the HRV between complex partial seizures/ focal seizures with psychogenic seizures and it illustrates that there is a greater ANS activation/dysregulation in patients with focal seizures when compared with psychogenic seizures.[14,17] Interestingly, a study reported that there is a high sympathetic tone before and during psychogenic seizures and a high vagal tone after the non-epileptic episode, thus demonstrating that autonomic dysregulation also accompanies certain types of psychogenic seizures.[21] However, there were no comparisons of HRV measures between different seizure semiologies. In this study, we compared the HRV metrics for focal seizures with impaired awareness, focal seizures with preserved awareness and generalized seizures. In earlier studies, there was a significant drop in HRV parameters like SDNN, RMSSD and pNN50 near or during seizures in patients with complex partial seizures; however, the drop was even more for patients having generalized seizures. These findings suggest that autonomic dysregulation can be increased during a generalized seizure when compared to focal seizure/ complex partial seizures. This is in concordance with the evidence that SUDEP is more associated with generalized seizures.[22] Autonomic dysfunction has been demonstrated in the interictal period and could be a potential biomarker for SUDEP.[23-25] Pathophysiology of SUDEP is multifactorial, autonomic dysregulation being the central theme.[26] The studied autonomic parameters could be clinically applied in patients with epilepsy to preemptively identify and abort such deadly complications.

It is also known, that there are certain seizure types, which demonstrate a higher autonomic dysfunction. Temporal onset or insular onset seizures are known to cause autonomic dysfunction. An Argentinian study compares changes in mean HR through the peri-ictal period for the temporal and extratemporal seizure; they also included the side of onset in their analysis.[22] They concluded that although tachycardia was most likely to be seen with temporal lobe epilepsy, it had no lateralizing value. Their study also lacks the use of time-domain HRV metrics. Our study compares temporal and extratemporal seizure for time-domain HRV metrics and we observe a statistically significant difference for RMSSD, SDNN and pNN50 when compared in the pre-ictal to ictal period. We also find a statistically significant difference, when we compared the HRV metrics for the side of onset, especially seizures with left-sided onset when compared with the right-side onset and bilateral onset. This comparison was most significant for RMSSD and SDNN when a comparison was made for these metrics, 20 minutes before the seizure and during the seizure. Contrary to the present study, animal models and past studies for lateralization shows the stimulation of the right hemisphere and inactivation of the left hemisphere may lead to greater sympathetic discharges and noradrenaline release and hence higher autonomic dysfunction. Hachinski *et al*.[23] demonstrated this asymmetry in stroke animal models. Zamrini's[24] groups found an increased HR after the inactivation of the left hemisphere by intracarotid injection of amobarbital, whereas a reduction in HR was seen after the inactivation of the right hemisphere.

Sweating, oxygen saturation and respiratory rate variability are some of the other autonomic parameters which can be studied. The autonomic changes associated with these parameters during an epileptic seizure can also be assessed, but the assessment of these parameters during an epileptic seizure has its limitations. For example, evaluation of respiratory rate variability like HRV can provide us with another mode of seizure prediction; however, respiratory rate sensors are sensitive and are more vulnerable to artifacts during a seizure.

Secondly, frequency domain measurement and nonlinear HRV measurements would have given us further insights regarding changes in HRV and we would advise directing future research in comparison to these parameters.

Thirdly, the persistence of minor artifacts is bound to cause a marginal variation in analysis and results, despite using maximum filters and artifact suppression techniques. Thus, we would suggest addressing these problems in future studies.

Fourthly, other confounding factors that could affect HRV parameters such as concomitant cardiac diseases, drugs, duration of epilepsy, and ongoing AEDs were not considered in this study.

Finally, our dataset was small and heterogeneous (in terms of age, gender, seizure location) to allow a meaningful subgroup analysis.

In conclusion, HRV analysis can be used as a valid method for quantifying central influences on the autonomic nervous system and its cardiac control. A major advantage of ECG-based seizure detection is that the ECG is an essentially easier signal to obtain, with a higher signal-to-noise ratio than EEG. In our study, we found that there was a statistically significant difference in HRV parameters in pre-ictal, ictal and postictal periods. The study also pointed out that there was a greater sympathetic activation and parasympathetic inhibition during an epileptic seizure in females as compared to male patients. Additionally, we also find that there is a significant difference in HRV metrics on comparing temporal and extratemporal seizures and the side of onset also has a significant association with autonomic dysfunction. The current study also suggests that time-domain parameters can be applied for the early detection of various types of seizures in patients with epilepsy. HRV measurements can be integrated into smart devices, HR monitors and ECG monitors which can help patients and doctors to stay alert and prepare for seizures and associated possible autonomic dysfunction. Furthermore, these systems can be made more effective by using a multimodal monitoring approach that also incorporates other biological signals.

ACKNOWLEDGEMENT

We thank EMU technologists for helping with data collection.

DISCLOSURE

Financial support: This study was supported by the seed grant for research from the Amrita Institute of Medical Sciences, India.

REFERENCES

1. Epilepsy facts and figures. *Epilepsy Foundation of America* 1999.
2. Fisher RS. Final comments on the process: ILAE definition of epilepsy. *Epilepsia* 2014;55(4): 492-3. doi: 10.1111/epi.12585.
3. Eggleston KS, Olin BD, Fisher RS. Ictal tachycardia: The head-heart connection. *Seizure* 2014;23(7):496-505. doi: 10.1016/j.seizure.2014.02.012.
4. Osorio I, Manly BFJ. Is seizure detection based on EKG clinically relevant? *Clin Neurophysiol* 2014;125(10): 1946-51. doi: 10.1016/j.clinph.2014.01.026.
5. Francesco B, Grazia BM, Emanuele G, *et al*. Linear and nonlinear heart rate variability indexes in clinical practice. *Computational and Mathematical Methods in Medicine* 2012; 2012: Article ID 219080. doi: 10.1155/2012/219080.
6. Malarvili MB, Mesbah M. Newborn seizure detection based on heart rate variability. *IEEE Transactions on Biomedical Engineering* 2009; 56(11):2594-603. doi: 10.1109/TBME.2009.2026908.
7. 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(2-3):195-202.
8. Kher R. Signal processing techniques for removing noise from ECG signals. 2019. DOI:10.17303/jber.2019.3.101.
9. Chavan MS, Agarwala RA, Uplane MD. Use of Kaiser window for ECG processing. *Proceedings of the 5th WSEAS International Conference on Signal Processing, Robotics and Automation*, 2006; vol. 2006, no. January 2006, 285-89.
10. Behbahani S, Dabanloo NJ, Nasrabadi AM, Teixeira CA, Dourado A. Pre-ictal heart rate variability assessment of epileptic seizures by means of linear and non-linear analyses. *Anadolu Kardiyoloji Dergisi (Anatolian Journal of Cardiology)* 2013;13(8):797-803. doi: 10.5152/AKD.2013.237.
11. Jeppesen J, Beniczky S, Johansen P, Sidenius P, Fuglsang-Frederiksen A. Detection of epileptic seizures with a modified heart rate variability algorithm based on Lorenz plot. *Seizure* 2015;24C,:1-7. doi: 10.1016/J.SEIZURE.2014.11.004.
12. Salahuddin L, Cho J, Jeong MG, Kim D. Ultra short term analysis of heart rate variability for monitoring mental stress in mobile settings. *Annual International Conference of the IEEE Engineering in Medicine and Biology - Proceedings* 2007; 2007:4656-9. doi: 10.1109/IEMBS.2007.4353378.
13. Mayer H, Benninger F, Urak L, Plattner B, Geldner J, Feucht M. EKG abnormalities in children and adolescents with symptomatic temporal lobe epilepsy. *Neurology* 2004;63(2):324-8. doi: 10.1212/01.WNL.0000129830.72973.56.
14. Opherk C, Hirsch LJ. Ictal heart rate differentiates epileptic from non-epileptic seizures. *Neurology 2002;*58(4): 636-8. doi: 10.1212/WNL.58.4.636.
15. Koenig J, Thayer JF. Sex differences in healthy human heart rate variability: A meta-analysis. *Neurosci Biobehav Rev* 2016;64:288-310. doi: 10.1016/j.neubiorev.2016.03.007.
16. Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. *Front Public Health* 2017;5: 258. doi: 10.3389/fpubh.2017.00258.
17. Ponnusamy A, Marques JLB, Reuber M. Comparison of heart rate variability parameters during complex partial seizures and psychogenic nonepileptic seizures. *Epilepsia* 2012;53(8):1314-21. doi: 10.1111/j.1528-1167.2012.03518.x.
18. Shaffer F, McCraty R, Zerr CL. A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. *Front Psychol* 2014;5:1040. doi: 10.3389/fpsyg.2014.01040.
19. Jeppesen J, Beniczky S, Fuglsang-Frederiksen A, Sidenius P, Jasemian Y. Detection of epileptic-seizures

by means of power spectrum analysis of heart rate variability: A pilot study. *Technology and Health Care* 2010;18(6):417-26. doi: 10.3233/THC-2010-0606.
20. Asadollahi M, Shahidi M, Ramezani M, Sheibani M. Interictal electrocardiographic alternations in patients with drug-resistant epilepsy. *Seizure* 2019;69:7-10. doi: 10.1016/j.seizure.2018.07.002.
21. Reinsberger C, Perez DL, Murphy MM, Dworetzky DA. Pre- and postictal, not ictal, heart rate distinguishes complex partial and psychogenic nonepileptic seizures. *Epilepsy Behav* 2012;23(1):68-70. doi: 10.1016/j.yebeh.2011.10.008.
22. Bozorgi A, Lhatoo SD. Seizures, cerebral shutdown, and SUDEP. *Epilepsy Currents* 2013;13(5):236-40. doi: 10.5698/1535-7597-13.5.236.
23. Massetani R, Strata G, Galli R, *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(3):363-9. doi: 10.1111/J.1528-1157.1997.TB01129.X.
24. Myers KA, Bello-Espinosa LE, Symonds JD, *et al*. Heart rate variability in epilepsy: A potential biomarker of sudden unexpected death in epilepsy risk. *Epilepsia* 2018;59(7):1372-80. doi: 10.1111/EPI.14438.
25. Ansakorpi H, Korpelainen JT, Suominen K, Tolonen U, Myllylä VV, Isojärvi JIT. Interictal cardiovascular autonomic responses in patients with temporal lobe epilepsy. *Epilepsia* 2000;41(1):42-7. doi: 10.1111/J.1528-1157.2000.TB01503.X.
26. Bozorgi A, Lhatoo SD. Seizures, cerebral shutdown, and SUDEP. *Epilepsy Currents* 2013;13(5):236-40. doi: 10.5698/1535-7597-13.5.236.