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Original Article

CARDIAC AUTONOMIC DYSFUNCTION IN PATIENTS WITH EPILEPSY

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ABSTRACT

Objective: The objective of this research was to appraise autonomic impairment through the examination of both time-domain and frequency-domain parameters of heart rate variability in individuals with epilepsy.

Methods: Thirty epilepsy patients and thirty healthy subjects were enrolled in our study for evaluation of autonomic functions, which was assessed by comparing heart rate variability between epilepsy patients and healthy subjects.

Results: There was no notable disparity observed in mean heart rate between the two groups. However, the frequency-domain metrics-LF Power, HF Power, and LF/HF ratio exhibited statistically noteworthy differences when comparing the patients to the control group (p-value<0.05). Conversely, parameters such as SDNN, RMSST, and pNN50 did not demonstrate statistically considerable differences in comparison to the controls (p-value>0.05). The parameters did not exhibit statistically significant distinctions between individuals with epilepsy for under 10 y and those diagnosed with epilepsy for over 10 y.

Conclusion: Our investigation revealed a notable contrast in HRV metrics between the patient group and the group of individuals in good health. The potential utilization of HRV as an indicator of susceptibility to SUDEP could enhance the quality of guidance provided to both patients and their families. Additional exploration is warranted, involving more extensive participant cohorts, and examining the impact of antiepileptic medications on HRV, within future studies.

Keywords: Autonomic function tests, Heart rate variability, Epilepsy, SUDEP

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INTRODUCTION

Epilepsy manifests as a condition where an individual experiences recurrent, unprovoked seizures. A seizure can be defined as a transient event marked by abnormal, excessive, or synchronized neuronal activity [1]. Roughly 50 million individuals worldwide are affected by epilepsy, making it one of the most widespread neurological disorders on a global scale. Nearly 80% of those grappling with epilepsy resides in low-and middle-income countries [2]. The mortality rate among epilepsy patients is 2-3 times higher than that of the general population. One of the epilepsy-related contributors to elevated mortality is Sudden Unexpected Death (SUDEP) [3].

SUDEP might arise due to an imbalance in the Autonomic Nervous System (ANS). The Autonomic Nervous System, with its sympathetic and parasympathetic components, plays a pivotal role in regulating Heart Rate Variability (HRV). Higher HRV is indicative of robust cardiovascular function, while lower HRV is linked to a notable risk of cardiovascular complications, including arrhythmias and silent myocardial infarctions, leading to SUDEP [4]. Although the precise cause of autonomic dysfunction in individuals with epilepsy remains somewhat unclear, alterations in the expression of cardiac ion channels and the adverse impact of cortical epileptic discharges on centrally governed cardiac responses are theorized as potential underlying pathophysiological elements [5].

Patients diagnosed with early-onset Temporal Lobe Epilepsy (TLE) may face a heightened susceptibility to cardiac dysfunction or arrhythmias compared to those with late-onset TLE. The HRV pattern observed in TLE patients is marked by an initial surge in sympathovagal influence preceding seizures, followed by a subsequent surge and sustained elevation in sympathetic activity throughout both the ictal and post-ictal phases [6].

SUDEP, being one of the contributors to mortality in epilepsy patients, lacks a singular mechanism. One theory proposes that it could be linked to autonomic dysfunction, which significantly contributes to patient demise through cardiac arrhythmias [3]. Elevated interictal epileptogenic activity might provoke an autonomic imbalance, resulting in altered neural discharges that lead to cardiac complications, possibly contributing to SUDEP [7].

A key driving force behind the eagerness to explore HRV in the context of epilepsy is the prospect of gaining deeper insights into SUDEP. This phenomenon is believed to be, in part, linked to autonomic dysfunction, and research has indicated a connection between SUDEP risk factors and more pronounced disturbances in HRV [8].

The assessment of autonomic imbalance involves autonomic function tests, among which the evaluation of heart rate variability stands as a direct and unintrusive approach. This involves either a brief 5 min recording or a more extensive 24 h recording to gauge cardiovascular health [9]. Hence, this study was undertaken to appraise autonomic dysfunction by scrutinizing both time-domain and frequency-domain parameters of heart rate variability in epilepsy patients.

MATERIALS AND METHODS

Study setting

The study was conducted by the department of pharmacology in collaboration with the Neurology Out-patient Department at PMSSY, BMCRI Bengaluru, Karnataka, India from December 2020 to Feb 2021.

Study design

This study was a prospective observational cross-sectional investigation.

Source of data

The cases that attended the outpatient clinic of the Neurology department at PMSSY, BMCRI Bengaluru, Karnataka, India, and diagnosed as a case of epilepsy were registered in the study.

Ethical approval

Following the approval from the Institutional Ethical Committee [No BMCRI/PS/254/2020-21 dated: 04/01/2021], the study was commenced, and written informed consent was procured from each participant. A total of thirty adult outpatients diagnosed with epilepsy were chosen at random to partake in this research. Likewise, thirty healthy individuals were enlisted to serve as the control group.

Inclusion criteria

Patients diagnosed with epilepsy aged 18-70 y of either sex taking treatment or willing to give informed consent were included in the study.

Exclusion criteria

Patients with cardiovascular co-morbidities, pregnant and lactating mothers and history of seizure due to trauma, infection or metabolic disorders were excluded. 30 patients were evaluated in the interictal period. Their demographic details, clinical evaluation, disease characteristics were recorded in the study proforma and similar data was collected from 30 healthy volunteers.

Measurement of HRV

The individuals underwent standardized Autonomic Function Tests (AFT) to evaluate their cardiac autonomic functions. Electrocardiogram (ECG) and blood pressure were monitored while the participants were in a supine position after a period of rest, as well as during regular breathing, for a duration of 5 min. The assessment of heart rate variability was conducted within a designated examination room. Prior to the procedure, patients were advised to abstain from consuming coffee, tea, and tobacco for a minimum of 2 h, and from consuming alcoholic beverages for a period of 24 h. ECG readings were taken for approximately 20 min, enabling the analysis of beat-to-beat heart rate variability. The initial ECG data was transformed into sequential R-R intervals, and the analysis was facilitated using Power Lab equipment and processed through Lab Chart 8 software.

HRV parameters

The selected parameters encompassed the following: Standard Deviation of all RR intervals (SDNN), the Square Root of the Mean of the Sum of the Squares of differences between adjacent RR intervals (RMSSD), pNN50, which corresponds to the percentage of consecutive RR intervals differing by more than 50 ms in a time-domain analysis of HRV. The frequency-domain HRV analysis included the quantification of High Frequency (HF) power (0.15–0.40 Hz) and Low Frequency (LF) power (0.04–0.15 Hz). Additionally, LF and HF were also presented in normalized units and expressed as a ratio.

Statistical analysis

The collected data was transferred to an Excel spreadsheet, where it underwent analysis. Descriptive statistics were employed, indicating measures such as mean and standard deviation. Parametric data were subjected to a two-tailed unpaired t-test, while non-parametric data were evaluated using the Mann-Whitney U-test. Categorical data were assessed using the Chi-square test. Statistical significance was determined when the p-value was less than 0.05.

RESULTS

Out of the 30 participants enlisted in the study, 23 were male, and 7 were female, spanning an age range from 18 to 70 y. The average epilepsy duration among the study's participants was roughly 6.4 y. Among the individuals recruited, 22 were under a single epilepsy medication regimen, while 8 were taking multiple medications. Table 1 demonstrates that there were no noteworthy distinctions in terms of age and gender distribution between the patient and control groups.

Table 1: Demographic detail of epilepsy group and control group

Demographic	Epilepsy group-n=30 mean (SD)	Control group n=30 mean (SD)	p-value
Age in Years	40.3(10.64)	24.07(2.12)	NS*
Duration of disease(Years)	6.47 (9.48)	-	-
Males	23	20	NS$
Females	7	10	
Pulse rate(bpm)	80.03(8.87)	79.17(12.12)	NS*
Systolic BP(mm Hg)	120.2(10.03)	122(12.68)	NS*
Diastolic BP (mm Hg)	80.07(8.27)	82.1(10.25)	NS*
Respiratory rate (cpm)	15.87(3.03)	19.47(1.76)	NS*

*un-paired t-test, $chi square test, NS=Not significant, Discrepancies in time-domain HRV metrics (SDNN 73 vs. 60, RMSSD 49 vs. 54, p NN50 12 vs. 21) did not reach a statistically significant threshold [table 2, fig. 1].

Table 2: Time-domain analysis of heart rate variability in patient with epilepsy and control

Time-domain	Patients	Control	p-value*
SDNN(ms)	73.48±52.55	60.91±12.86	0.645
RMSSD(ms)	49.03±25.42	54.47±14.14	0.710
pNN50(%)	12.32±7.21	21.44±7.58	0.086

*Mann-Whitney U test, P-value<0.05 was considered statistically significant, Abbreviations-SDNN, a standard deviation of NN interval; RMSSD, root mean square of standard deviation, pNN50-Percentage of NN50 count of all RR intervals

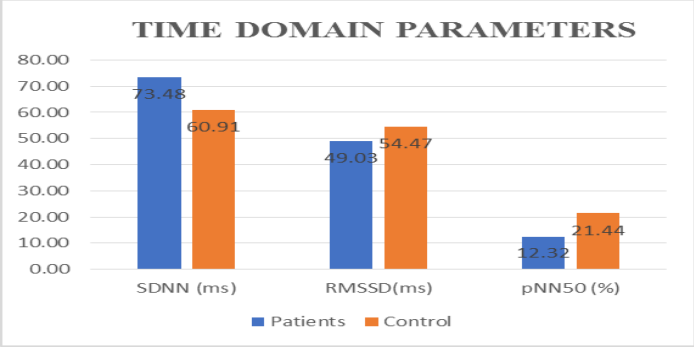

Fig. 1: Showing a bar graph comparing time domain parameters of HRV between patients and controls, the frequency-domain parameters, LF Power, HF Power, and LF/HF ratio of the patients show statistically significant variations in comparison to controls (p-value<0.05) [table 3, fig. 2]

Table 3: Frequency domain analysis of heart rate variability in patients with epilepsy and control

Frequency domain	Patients	Control	p-value $
LF Power (nu)	64.54±14.12	48.33±5.5	*0.039
HF Power (nu)	38.77±7.37	50.26±5.45	*0.015
LF: HF ratio	2.28	1.16	*0.004
TP (ms)	2626.83±2111.42	5118.01±2728.89	0.154

$Mann-Whitney U test, *P-value<0.05 was considered statistically significant, Abbreviations: LF, low frequency; HF, high frequency; LF/HF-Ratio of LF-to-HF. TP-Total power

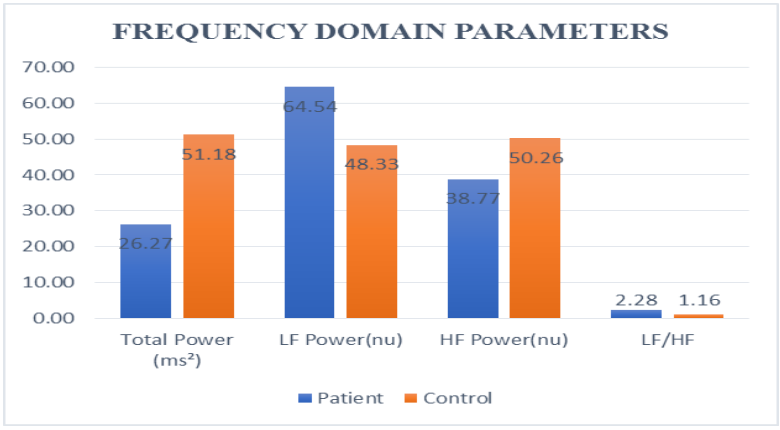

Fig. 2: Showing a bar graph comparing frequency domain parameters of HRV between patients and controls

DISCUSSION

Heart rate variability (HRV) pertains to the rhythmic fluctuation in heart rate between successive beats, originating from the intricate interplay of sympathetic and parasympathetic nerve fibers that influence the sinoatrial node [10]. Autonomic dysfunction can manifest in individuals grappling with temporal lobe epilepsy or type 2 diabetes mellitus, even in the absence of neuropathy. Employing a 5-min assessment of HRV emerges as a pivotal technique for uncovering concealed cardiac autonomic neuropathy (CAN) [11, 12]. The influence of seizures on the onset of cardiac autonomic neuropathy (CAN) has been implicated in instances of sudden unexpected death in epilepsy among those with the condition [5].

The study population comprised both males and females, with a male predominance, and the mean age of patients stood at 40 y. The average duration of the disease was documented as 6.47 y. The assessment of autonomic function unveiled that HRV measurements were higher in male patients as compared to female patients, suggesting an increased level of sympathetic activity. However, this elevation did not achieve statistical significance. Another investigation indicated a marked reduction in HRV among healthy women in comparison to healthy men. Previous research also displayed a decline in HRV correlated with advancing age, accompanied by gender-related distinctions [13].

Among grown-ups grappling with generalized epilepsy, the collective body of evidence suggests an anomalous state of HRV. Discoveries pointing to an alteration during interictal periods towards a prevalence of sympathetic control have been documented in the context of mature individuals afflicted with juvenile myoclonic epilepsy and epilepsy marked by generalized tonic–clonic seizures [14].

Spectral analysis has been documented as a technique capable of delineating autonomic activity, while the HF frequency range corresponds to parasympathetic (vagal) regulation [15]. This study successfully exhibited a notable statistical discrepancy in frequency domain parameters, showcasing those patients exhibited an elevated LF value, a diminished HF value, and an augmented LF/HF ratio in comparison to the control group. Concerning the time domain, SDNN, RMSSD, and pNN50 values were higher among patients than controls; however, this disparity didn't achieve statistical significance. These findings suggest an escalation in sympathetic activity and a reduction in parasympathetic activity as highlighted by the frequency domain analysis. This shift in autonomic activity might be accountable for an amplified susceptibility to SUDEP in individuals affected by epilepsy.

In a recent investigation conducted by Mativo and colleagues [16], the assessment of RMSSD in the time domain demonstrated a considerable reduction in measurements among individuals with generalized tonic-clonic epilepsy when compared to the control group. Additionally, the frequency domain analysis unveiled diminished total power (TP) and high-frequency (HF) values in the patients. These observations diverge from our own study, where we identified elevated RMSSD, increased LF, and decreased HF values. This variance in findings might stem from disparities in the methodology employed.

Regarding temporal lobe epileptic patients, both the 24-hour HRV measurements and the awake HRV investigations indicated reduced values, encompassing parameters such as variance, HF, LF, and the LF/HF ratio, when juxtaposed with healthy controls of similar age. These outcomes propose a transition towards sympathetic predominance [17]. In a study involving hot water epilepsy, utilizing 5-min awake electrocardiography (ECG) recordings, diminished RMSSD and HF, as well as heightened LF and LF/HF ratio, were detected, providing evidence of a transition towards sympathetic predominance [18].

According to Persson and colleagues [19], no discernible alterations in HRV parameters were noted among newly diagnosed epilepsy patients when contrasted with healthy controls. The divergence in inclusion criteria, a lengthier disease duration, and the incorporation of untreated seizure patients might have contributed to the dissimilarities in findings between our respective studies.

As indicated in a study conducted by De Giorgio and colleagues, aimed at identifying risk factors, it was revealed that RMSSD values exhibited a positive correlation with the susceptibility to SUDEP [20]. In another investigation by Nashef and co-authors, the proposal was put forth that malfunction within the parasympathetic system could potentially lead to occurrences of central apnea, arrhythmias, and cardiac failure. Detecting autonomic impairment at an early stage would contribute to the prevention of SUDEP [21]. The precise mechanism through which autonomic dysfunction heightens the risk of SUDEP remains elusive. Research conducted by Myers and

colleagues [22] offers insights indicating that autonomic dysfunction correlates with the risk of SUDEP among epilepsy patients with sodium channel mutations.

The current investigation exhibited strengths in its cost-effectiveness and simplicity, which were facilitated by the utilization of a cross-sectional study design. Additionally, the incorporation of healthy controls served to minimize potential errors stemming from device calibration. Employing a time-domain parameter streamlines the analysis procedure, circumventing potential complications associated with discrepancies in Fourier transform protocols that are requisite for frequency domain analysis. However, the study had certain limitations. These included a relatively small sample size, data collection conducted prior to the commencement of antiepileptic treatment, and the lack of HRV data during follow-up visits. Addressing these limitations would likely have resulted in a more accurate and comprehensive response to our research inquiry.

Further exploration into the clinical implications of the correlation between altered HRV and SUDEP is warranted. The utilization of HRV measurements to establish normal and anomalous ranges could potentially serve as a SUDEP risk index, thereby augmenting clinicians' capability to provide informed counseling to patients and their families regarding the probability of SUDEP. If HRV proves to be a dependable biomarker for SUDEP, specific therapies might aid in monitoring and could potentially yield beneficial effects on patients.

CONCLUSION

We effectively showcased a noteworthy divergence in HRV parameters between patients and the group of healthy volunteers. Research endeavors in the domain of HRV within the context of epilepsy will pave the way for a seamless transition from the realm of research to practical clinical applications. Further exploration, employing more extensive participant cohorts, is imperative to scrutinize the impact of antiepileptic medications on HRV.

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AUTHORS CONTRIBUTIONS

All the authors Rashmi H, Dr. Praveen Panchaksharimath, Dr. Rohith V have equally made a substantial contribution to the conception, acquisition of data, interpretation of data and in drafting the article and agreed to be held accountable for all aspects of the work.

CONFLICT OF INTERESTS

Declared none

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