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Original Research Article

ASSESSMENT OF CARDIOVASCULAR AUTONOMIC FUNCTIONS IN PATIENTS PRESENTING WITH SEIZURE AND EPILEPSY DURING INTERICTAL PERIOD

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Abstract

Background: Patients of seizure and epilepsy presented with different cardiovascular autonomic profiles (associated with imbalance of sympathetic and parasympathetic activity) predisposition to cardiovascular dysfunction and SUDEP for this the heart rate changes in ECG, parasympathetic and sympathetic autonomic function testscan be helpful. Material and Method: Current study was hospital based descriptive epidemiological study Cross-Sectional in design which included 200 patients presented with history of seizures and epilepsy from OPD and IPD of RNT Medical College and Attached Group of Hospital, Udaipur (Rajasthan) in age group of 18-65 years (both genders).Resting heart rate, parasympathetic (E/I ratio, VM ratio and L/S ratio) and sympathetic (BP response to postural change and isometric hand grip work) autonomic tests were simultaneously recorded in Lead-I ECG of MPEG-4, Allengers Global Health care video EEG systemduring interictal duration (within 15 days from last attack). Result: The mean age at onset of disease was 33.02 ± 13.9 years, resting heart rate was 80.52±17.59 bpm, E/I ratio was 1.16±0.07, VM ratio was 1.30±0.18and 30:15 standing ratio was 1.09±0.06 in patients of seizure and epilepsy. The systolic/ diastolic blood pressure in patients from Supine to standing was 125.4±10.8/80.6±7.43 to 114.8±7.1/93.3±11.48mmHg with orthostatic difference of ↓12.5±4.75/↑13.4±4.7. Systolic/ diastolic blood pressure response during hand grip strain was 150.5±14.4/100.35±10.6 mmHg and after release from strain was 127.7±10.2/82.13±6.79mmHg with difference of 22.86±4.88/18.77±3.5 mmHg. Above data determines that the mean value of heart rate, parasympathetic and sympathetic variables in patients was obtained with in normal limit. Whereas Cardiovascular parasympathetic function test variables (E/I ratio, VM ratio and 30:15 standing ratio) were significantly ($p<0.001$) altered in different types of epilepsy and seizure. The diminished VM ratio and 30:15 standing ratio were obtained in epilepsy patients. The E/I was on lower side of normal. Increased heart rate and reduced ratio of parasympathetic function test variables significantly (<0.001) changed with longer duration of disease and higher frequency of seizure. Blood pressure changes had statistically significant ($P<0.05$) to different types of seizure and epilepsy, maximum increase in diastolic blood pressure from supine to standing position and in handgrip test was obtained in patients of epilepsy followed by GTCS and unclassified seizure disorder. The difference of systolic and diastolic BP response from supine to standing and isometric handgrip test had significantly altered ($p<0.001$) with duration of disease and frequency of seizure ($p<0.05$),

rise in systolic and diastolic blood pressure from supine to standing position found in longer duration of disease higher frequency of attack per month. **Conclusion:** In different aspect of disease, the increase in overall heart rate and decrease in E/I, VM, L/S ratio from normal values accomplished lower parasympathetic activity in patients, the higher diastolic blood pressure in hand grip test exhibits increased sympathetic activity. Therefore, present study suggested that interictal cardiovascular autonomic dysfunction in epilepsy patients may be due to imbalance between lower parasympathetic and higher sympathetic tone, which further predisposed at risk for SUDEP.

INTRODUCTION

The International League Against Epilepsy ILAE determine "anEpilepsy or seizure, one of the most common and serious brain disorders, characterized by spontaneous and stereotyped disturbance of sensation, behavior, emotion, or motor function resulting from the rapid and local discharges of gray matter". Seizures with symptoms occur in the acute state (provoked seizure) or in epilepsy (two or more unprovoked seizure).[1]This disorder is heterogenic in nature with idiopathic (genetic basis), symptomatic (identified brain injury) and cryptogenic (unknown) aetiologies. It affects more than 50 million people worldwide and half of them are children. However, the incidence of epilepsy is more common in the developing countries than in the developed ones with a prevalence rate of 24 to 53 per 1,00, 000 population in developed countries.[2]

The prevalence rate of disease in India is 2.5-11.9 per 1,000 population per year, which increase by incidence of 0.28-0.53 per 1,000 population per year 3and the prevalence rate in Rajasthan is 3.0 per 1,000 population per year.[3,4]Epilepsy is not only a personal burden to the individual, but it is also an economic burden due to direct costs like antiepileptic drugs (AEDs) and surgery, hospitalization for seizures, comorbidities, and also indirect costs attributable to reduced school attendance, employment and productivity losses, and caregiver burden.[5]

The recruitment of the central autonomic network during seizure propagation is mediated by the extensive connections, throughout the brain and brainstem and it has presumed that abnormality of neuronal networks in patients with seizure or epilepsy. If widespread and localised abnormal and synchronised electrical discharge seen in seizure or epilepsy occurred with some form of central and peripheral autonomic dysfunction. The dysfunction of autonomic nervous system associated with seizures, varies from subtle to gross alterations. In epilepsy, the signs of autonomic nervous system dysfunction are often over shadowed by the more apparent motor and higher cerebral effects of seizures, but autonomic disturbance is a common feature of many seizure types (Ansakorpi et al. 2000; Ansakorpi et al. 2002a).Disturbances of autonomic functions with subsequent cardiac arrhythmias due to the effects of recurrent seizures on cardiac microstructure.[6]

Epilepsy has a significant economic impact on health-care needs, premature death, and disruption of work or education for individuals and their families.On behalf of this current study tries to simplify the involvement of autonomic changes by measurement of physiological variables (reflexes), which are controlled by ANS. The measurement of the heart rate from a simultaneously running electrocardiographic (ECG) record with EEG and recording of systemic arterial blood pressure were reliable and reproducible, simple, quick to carry out and all non-invasive for the early detection of autonomic dysfunctions by parasympathetic and sympathetic function test, which may result in a better understanding of the cardiovascular effects in epilepsy and help to developed strategies for prevention of SUDEP.

MATERIALS AND METHODS

Present study was conducted on 200 patients presented with history of seizures and epilepsy from OPD and IPD attending EEG laboratory of Neurology department RNT Medical College and Attached Attached Group of Hospital, Udaipur (Rajasthan).We were included both sexes in between the age of 18-65 years from February 2023 to July 2023 after approval from IRB, ethical committee and Research Board Rajasthan university (No.RNT/ACAD./IEC/2022/288, Dated:-13.09.2022).Current study was hospital based descriptive epidemiological study Cross-Sectional in design. a) Inclusion Criteria:(i) Those patients who were diagnosed with seizure and epilepsy and not taking any medications other antiepileptics (ii) No intramuscularly injections were administered and there was no previous history of neuromuscular disease in any patient (iii) Written consent was obtained from the subjects and their attenders at the time of data collection. b) Exclusion Criteria: (i) Patients having history of diabetes mellitus and hypertension. (ii) Patients who were alcoholics and active smokers of bidi/cigarette. (iii)Those patients who had history of medical disease such as myocardial infarction, Percutaneous Coronary Intervention (PCI). (iv) Patients with clinical signs of autonomic dysfunction. (v) Patients had history of recurrent infections, muscle injuries, allergic reactions or having any recent acute infection. (vi) Pregnant women, lactating mothers, PCOD and PCOS patients and patients ingesting synthetic oral contraceptive pills (OCP). (vii) Those patients who

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were not willing to participate and had not given inform consent for study.

Procedure: In current study the clinical history of signs and symptoms, history of disease duration, frequency of seizure and attack duration of seizure was obtained from patients which was followed by video EEG of 20mins through MPEG-4, Allengers Global Health care system, India during interictal period (15 days from the last attack of a seizure). Standard 1-channel ECG was simultaneously recorded in conjunction with the EEG by using I leads. Bipolar ECG leads were placed on both right and left hand at wrist among them one was referral and other one active electrode. The rate and voltage of the ECG recording was 25 mm/s and 1 mV/cm, respectively, with a frequency range varying from 0.8 to 60 Hz. In two hundred patients of present study heart rate was recorded by lead Iof ECG considered as baseline if basal HR in between 60 to 100beats/min, bradycardic if their basal HR is less than 60 beats per minute or tachycardic if their basal HR is greater than or equal to 100 beats per minute.[7]

A. Parasympathetic Function Test

B. Sympathetic Function Test

A.Parasympathetic Function Test:[8]

(i)Heart Rate Variation With Respiration (Deep Breathing) Inspiration increases the heart rate and expiration decrease it, this phenomenon is primarily mediated by the vagal innervation of heart, thus indicated for testing the integrity of parasympathetic functions.

Procedure:(a) The subject to lie supine quietly on a couch with sphygmomanometer and ECG leads attached.(b) Record the resting ECG and measure the base line HR.(c) The subject has been instructed to inhale deeply for 5 seconds and then exhale for next 5 seconds repeat this at least for six cycles for one minute, mean while we were recorded his/her ECG in both stages. (d) Determine the maximum and minimum heart rate during deep breath with each respiratory cycle. (e) Determine the expiratoryto inspiratory (E/I) ratioby longest R-R intervals in expiration to shortest R-R intervals in inspiration shows in ECG readings of each patient.

The Average E/I ratio of six cycles in normal young individuals is less than 1:2 and in autonomic dysfunction E/I ratio is more than 1:2.Normal range is ≥1.07-1.23(16-65years). Less than 1.07 is abnormal.

(ii) Valsalva Manoeuvre Heart Rate Changes: The Valsalva ratio was measure of parasympathetic and sympathetic function.

1. In Valsalva maneuver (VM) named after scientist AM Valsalva who describe it, parasympathetic is the afferent and the efferent, and sympathetic is the part of the efferent pathway. Therefore, Valsalva ratio assesses more of parasympathetic (cardiovagal) than sympathetic function.Valsalvamanoeurve (i.e. forced expiration against resistance) is a simple test done to asses baroreceptor integrity. Changes in the intra-arterial BP have been used previously to assess the response to the VM. However, heart rate changes have also been shown to be reliable and have the advantage of being non-invasive.

Valsalva Manoeuver has 4 phases:

a) Phase I occurs at the onset of strain. There is transient rise in BP (without any change in heart rate) due to an increase intrathoracic pressure.
b) Phase II occurs during straining. Initially venous return decrease resulting in fall in cardiac output and BP. This inhibits the baroreceptors producing tachycardia and peripheral vasoconstriction. As a result, BP returns towards normal. The HR increase steadily throughout the phase due to vagal withdraw initially and increased sympathetic activity in the later stage,
c) Phase III occurs following the release of strain which results in transient decrease of BP without change in HR. this is due to intrathoracic pressure returning to normal causing the displacement of blood to pulmonary vascular bed.
d) Phase IV occurs with further cessation of strain. The BP slowly rises to reach above baseline level secondary to pheripheral vasoconstriction, called overshoot phenomenon. This stimulates the broreceptors producing bradycardia and drop in BP normal level.

Procedure

a) Explain the procedure to the subject to get maximum cooperation.
b) The subjects were made to lying comfortably on a couch with sphygmomanometer and ECG leads attached to his/her arms. Allow them to relax and measure baseline HR and BP.
c) Then nose was clipped with the help of a nose-clip and insert a mouth piece of Sphygmomanometer between the teeth and lips.
d) Connect the other end of the mouthpiece to a mercury manometer.
e) Ask the subject to strain by blowing against closed glottis into the mouthpiece attached to the manometer and maintaining a pressure of 40mmHg for 15sec.
f) A continuous ECG was recorded 1 minute before the manoeuvre (resting period), during the manoeuver (strain period, 15sec) and 45seconds following stain release.
g) Repeat the procedure three times with a gap of 5minutes between the manoeuver.

Valsalva ratio was taken as ratio of maximum HR during the strain (phase II) to the minimum HR after the strain (phase IV). Alternatively, this has been also be calculated as:

Longest R-R interval after the strain (phase IV)/Shortest R-R interval during the strain (Phase II)

The maximum Valsalva ratio of three trails was taken for the autonomic activity. A ratio of greater than 1.45 is normal, 1.20 to 1.45 is borderline and less than 1.20 is abnormal (autonomic disturbances).Clinical significance: failure of HR to increase during strain suggests a sympathetic

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dysfunction and failure of HR to slow during BP overshoot suggests a parasympathetic disturbance.

(iii) Orthostatic Heart Rate Change

Orthostatic heart rate changes have been recorded by instructing the subject to lie down on examination couch in relax state then instruct him/her to stand up immediately from supine position. The ECG has been recorded in both the stages. Changing in posture from supine to standing, heart increases immediately by about 10 to 20 beats per minutes.

(a) On standing, the heart rate increases until it reaches a maximum at about the 15th beat, after which it slows down to a stable state about 30th beat. (b)The ratio of R-R intervals corresponding to the 30th and 15th heart beat is called 30:15 ratio.In ECG probingthe ratio of the longest RR interval in standing around beat 30 (slowest HR beats 20-40) to the shortest RR interval in standing around beat 15 (fastest HR beats 10- 20) after lying was used as the "30:15 ratio." 30:15 ratio is considered a measure of cardiac vagal function.

The normal 30:15 ratio is 1.15-1.12 at 21 to 30 years and 1.12 to 1.10 at 31 to 40 years of age. Ratio less than 1.04 is considered abnormal.

B. Sympathetic Function Test:[9]

(i)Orthostatic Blood Pressure Changes

Orthostatic blood pressures changes had been recorded by instructing the subject to stand up immediately from supine position then record his/her blood pressure immediately in standing position by auscultatory method. The difference between BP (systolic and diastolic BP) lying and the BP (systolic and diastolic BP) standing has been calculated.Normally the blood pressure falls and returns to normal within 15-60 seconds by activation of baroreceptor reflex. When there was sustain fall in systolic more than 20mmHg and raise in diastolic more than 10 mmHg consider as sympathetic insufficiency.

(ii)Hand Grip Test (HGT) for Blood Pressure Response to Isometric Exercise

Isometric exercise produces a significant rise in BP and HR, which was easily elicited by using sustained handgrip test. The response is reflex in nature and is due to increased peripheral resistance and increased cardiac output.

The BP rises by peripheral vasoconstriction mediated any damage to the neurological pathways involved could lead to a diminished or an absent cardiovascular response to sustain handgrip. The value of more than 15mmHg rise in diastolic as borderline and 10mmHg or less is abnormal an indicator of sympathetic insufficiency.

Procedure

a. Explain the details of test procedure to the subject and record the baseline BP with the help of sphygmomanometer.
b. Ask the subject to hold the dynamometer in right hand (or dominant hand) to have a full grip of it.
c. Then instruct him to compress the handgrip dynameter with maximum effort. Measure the tension developed wait for one minute.
d. Repeat the whole procedure twice and take the 2nd and 3rd reading.
e. Take mean (or highest) of three readings, this is referred as maximal isometric tension (Tmax).
f. Thentold the subject to maintain a pressure of 30% ofTmaxfor 5min.
g. During the test procedure, record the BP every 30 seconds with the help of sphygmomanometer on the non-exercising arm.
h. The rise in diastolic BP at the point just before the release of handgrip has taken as the index of response to handgrip test.

The difference between the highest diastolic BP just before the contraction was released, and the handgrip started was taken as a measure of the response.

The normal range in diastolic blood pressure more than 15mmHg and rise in heart by about 30%.The blood pressure raises due to increase in sympathetic activity and heart rate rise due to decrease in parasympathetic activity.

Statistical Analysis: Statistical evaluation was done by using statistical software SPSS version 24. Results of Quantitative variables were presented as the Mean ± Standard Deviation (SD) analyzed with independent Student's t-test (for less than two sample) and ANOVA (more than two samples). Categorical variables (qualitative data) were expressed as counts and percentages and analyzed with Chi-square test. Correlations between different quantitative variables were performed with two-tailed Pearson's correlation analysis. For all the tests, a significant level of statistics was considered when p value was less than 0.05 and highly significant were $p<0.001$.

RESULTS

[Table 1] Normal range of heart rate is 60-100beats per minutes. In patients heart rate ranges from 46-125beats/min with mean value of80.52±17.59beats/min. Normal rangeof E/I ratio is ≥1.07-1.23(16-65years) and less than 1.07 is abnormal. VM ratio of greater than 1.45 is normal, 1.20 to 1.45 is borderline and less than 1.20 is abnormal.Normal range of 30:15 ratio is 1.15-1.12 (21 to 30 years, 1.12 to 1.10 at 31 to 40 years of age). 30:15 standing ratio less than 1.04 is considered abnormal.In patient's E/I ratio ranges from 1.02-1.23 with mean value of 1.16±0.07, VM ratio obtained from 0.78-2 range with mean value of 1.16±0.07 and the range of 30:15 standing ratio was from 1-1.3 with mean value of 1.09±0.06.

In present study the mean value of heart rate, parasympathetic and sympathetic variables in patients was obtained with in normal limit.

[Table 2] The Heart rate was recorded by lead I of ECG in 200 patients of seizure and epilepsy, among

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them the heart rate of below 60 beats/min (Bradycardia) in 31 patients (15%), 150 patients (75%) had obtained between 60 to 100beats/min and 19 patients had reported more than 100beats/min (tachycardia) of heart rate.

[Table 3] The E/I ratio hadevaluated 1.14±0.05 in female and 1.06±0.07 male patients of seizure and epilepsy with p value of 0.577.VM ratio hadidentified 1.30±0.19 in female and 1.28±0.18 in male patients(p value of 0.987).In present study heart rate response to standing (30:15 ratio)had obtained 1.07±0.05 in female and 1.09±0.06 in malepatients of seizure and epilepsy with p value of 0.399.There was in-significant difference in parasympathetic function test among female and male patients.

In present study the difference of systolic/ diastolic blood pressure from supine to standing position had found 10.8±4.4/13.0±4.2 mmHgin female and 10.0±4.4/12.2±4.5 mmHg in male patients with p value of 0.214 and 0.227. The difference of systolic/diastolic blood pressure just before and after hand grip release from hand grip dynameter had obtained 23.1±5.0/18.7±4.8 mmHg in female and 22.5±4.9/17.9±4.6 mmHg in male patients (p value of 0.397 and 0.222).There were no-significant differences in BP response among male and female patients.

[Table 4] EI ratio, VM ratio and 30:15 standing ratio had obtained 1.16±0.07,1.30±0.18 &1.09±0.06 in patients between the age of 18-25 years, 1.14±0.07,1.26±0.16 &1.08±0.07 in age of 26-35 years, 1.15±0.07, 1.29±0.20 &1.08±0.06 in age of 36-45 years, 1.17±0.06,1.27±0.20&1.09±0.08in age of 46-55 years and 1.19±0.04,1.41±0.17 &1.12±0.05 above the age of 55 years with p value of 0.092,0.039&0.32.

There were in-significant changes in E/I ratioand 30:15 standing ratio (p=0.092, 0.32) with different age groups of patients. The significant variations were obtained in VMratio (p<0.039).

In present study the difference of systolic/diastolic blood pressure from supine to standing positionand pressure just before and after hand grip releasehad obtained

9.9±4.2/12.1±4.0&22.5±4.9/18.2±4.9mmHg in patients within age of 18-25 years, 11.3±4.3 /13.3±4.2 and 23.4±5.0/18.9±4.3 mmHg sec in 26-35 years of age, 9.9±4.9/12.9±4.8&22.6±5.3/17.4±5.0 mmHg in those patients who were in between age of 36-45 years, 11.4±4.8/13.5±5.0 &24.0±4.7/18.8±4.5 mmHg had reported in age of 46-55 years and 8.7±3.9/10.4±3.9&21.1±4.3/17.1±4.6 mmHg above the age of 55 years (p value of 0.119,0.083, 0.333 and 0.522).

There were no-significant differences (p>0.05) in blood pressure response with different age groups of patients.

[Table 5] The heart rate variation in different types of diagnosis wasobtained 81.35±20.44 beats/min in epileptic patients, 89.48±22.34 beats/min in patients of generalised myoclonic epilepsy, 80.37±17.31 beats/min was evaluating in generalised tonic clonic seizure patients and 78.67±15.85 beats/min in patients presenting with seizure disorder with p value of 0.145.In manner of differential diagnosis, the E/I ratio,VM ratio and 30:15 standing ratiowas found 1.09±0.06&1.09±0.09 1.01±0.02 in patients of epilepsy other than GME, 1.11±0.07,1.16±0.11 &1.05±0.06 in patients of recurrent generalised myoclonic epilepsy, 1.16±0.07, 1.29±0.15&1.09±0.06 in patients of single onset generalised tonic clonic seizure and 1.19±0.05,1.37±0.18 &1.11±0.05 in patients of unclassified seizure disorder with p value less than 0.001.

Cardiovascular parasympathetic function test variables(E/I ratio, VM ratio and 30:15 standing ratio) were significantly (p<0.001) altered in different types of epilepsy and seizure.The diminishedVM ratio and 30:15 standing ratio were obtained in the patient's epilepsy other than GME. The E/I was on lower side of normal. VM ratio was also diminished in patients of recurrent GME.

In various types of seizure and epilepsy the mean difference of systolic/diastolic blood pressure from supine to standing position and just before and after hand grip release from hand grip dynamometerhadevaluate

11.7±5.1/14.0±5.7&24.8±6.8/19.0±4.1 mmHg in patients of epilepsy other than GME, 12.9±5.7/15.2±5.6 &25.4±6.9/20.2±3.1mmHg in patients presented with recurrentgeneralised myoclonic epilepsy, 10.4±4.4/12.7±4.1 &22.9±4.8/18.1±3.2 mmHg in patients related tosingle onset generalised tonic clonic seizure and 9.5±3.8/11.6±3.7 &21.8±3.8/17.8±3.8 mmHg in unclassified seizure disorder patients (p value of 0.014, 0.0060.01 and 0.022).

In patients of seizure and epilepsy blood pressure from supine to standing position had determine, fall in systolic and raise in diastolic blood pressure more than 10mmHg in patients of GME which was followed by epilepsy, GTCS and seizure disorders patients respectively.

According to the index of handgrip test the normal range in diastolic blood pressure more than 15mmHg.

Present study evaluates difference of diastolic blood pressure just before and after hand grip release from hand grip dynamometertest had shown raiseddiastolicblood pressure more than 15 mmHg which revealedhigher sympathetic activity (p<0.05) in patients of seizure and epilepsy.

Above table explain that blood pressure changes in various sympathetic function tests had statistically significant (P<0.05) to different types of seizure and epilepsy, maximum increase in diastolic blood pressure from supine to standing position and in handgrip test was obtained in patients of GME followed by epilepsy, GTCS and unclassified seizure disorder. [Table 6] In present study the heart rate was evaluated 76.69±15.04 beats/min within a

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disease duration of 1 month, 79.23±14.13 beats/min in disease duration of 1-12 months, 78.03±17.51 beats/min in duration of 24-60 months, 79.48±20.20 beats/min in 72-120 months of disease, 89.35±20.42 beats/min in duration of 132-240 months, 8.280±24.39 beats/min when patients reported disease duration more than 240 months and 93.85±17.18 beats/min in patients suffered from birth with p value of 0.011.

The EI ratio, VM ratio and 30:15 standing ratiowas obtained 1.20±0.04,1.47±0.15&1.12±0.05 within a disease duration of 1 month, 1.19±0.06,1.40±0.16& 1.11±0.06 in disease duration of 1-12 months, 1.16±0.07, 1.28±0.14& 1.11±0.06in duration 24-60 months, 1.13±0.07, 1.17±0.07 &1.04±0.05 in 72-120 months of disease, 1.11±0.07,1.12±0.11& 1.05±0.05in disease duration of 132-240 months, 1.13±0.05,1.13±0.02& 1.02±0.02 where history disease duration had more than 240 months and 1.11±0.07, 1.13±0.05 &1.02±0.01 when patients suffered from disease by birth (p value less than 0.001).

Above table shows that heart rate, cardiovascular parasympathetic function test variables were significantly (<0.001) changed with duration of disease, increased heart rate and reduced ratio of parasympathetic function test variables in patients who were identified with longer duration of disease (birth, >240 months and 132-240 months).

In patients of seizure and epilepsy the difference of systolic/diastolic blood pressure from supine to standing position and just before hand grip release and prior to handgrip test started from handgrip dynameter had obtained 8.4±2.8/10.5±2.5&21.0±3.2/17.1±3.4mmHg within a month of disease, 8.6±3.4/10.7±3.1&22.2±3.8/18.6±3.2mmHg in disease duration of 1-12 months, 10.4±4.0/10.7±3.1&21.9±4.1/17.4±4.5mmHg in duration of 24-60 months, 10.8±5.4/12.5±3.9&22.6±5.9/17.1±5.7mmHg in 72-120 months of disease, 12.9±5.1/13.3±5.0&26.1±6.4/20.7±6.2mmHg in disease duration of 132-240 months, 13.3±6.4/16.0±5.3&29.3±1.2/22.0±0.10mmHg whereperiod of disease had more than 240 months and 14.7±4.1/17.1±4.3&27.0±5.9/21.3±5.8mmHg when patients suffered from disease from birth (with p value less than 0.001).

The systolic and diastolic BP response to supine to standing difference and thediastolic BP response to isometric handgrip test had significantly altered (p<0.001) with duration of disease, rise in systolic and diastolic blood pressure from supine to standing position found in longer duration of disease.

[Table 7] The heart rate had obtained 77.91±15.93 beats/min in patients who were reported 1st time for seizure attack, 85.63±17.78 beats/min when attack had experienced 1-2 times per month, 74.55±17.16 beats/min where seizures had carried out 3-5 times per month, 79.65±14.11 beats/min when frequency of attack had 6-12 times attack per month and 83.51±16.85 beats/min where frequency of attack had 11-20 times per month with p value of 0.003.

In accordance frequency of seizure per month the EI ratio, VM ratio and 30:15 standing ratiohad calculated 1.19±0.04, CD1.46±0.16& 1.12±0.05in patients after single attack, 1.15±0.07,1.26±0.17 &1.08±0.07 when patients explain seizure attack 1-2 times per month, 1.16±0.07, 1.28±0.15& 1.09±0.06 where seizure had described 3-5 times per month, 1.16±0.06, 1.38±0.21 &1.10±0.06 where attack had experienced 6-12 times per month and 1.16±0.06, 1.17±0.16 &1.05±0.06bhad obtained in seizure frequency of 11-20 times per month with p value of 0.042,<0.001 &0.004.

Above data implies that cardiovascular parameters were significantly (p<0.05 &<0.001) altered with frequency of seizure per month, increases the heart rate and decreases the parasympathetic parameters in patients with greater number of seizures per month.

In accordance of seizure frequency per month the difference of systolic/ diastolic blood pressure from supine to standing position and just before hand grip release and prior to handgrip test started from handgrip dynamometer had obtained 8.6±2.7/10.6±2.5&21.4±3.2/17.6±3.4mmHg those who were reported 1st time for seizure attack, 11.4±4.3/13.5±4.3&23.8±5.0/19.1±4.3 mmHg when attack had experienced 1-2 times per month, 9.4±4.7/11.9±4.5&21.4±5.1/16.6±5.2 mmHg when frequency of attack had 3-5 times in a month, 10.0±4.6/12.0±4.6&23.3±3.8/19.0±4.0mmHg where seizures had carried out 6-12 times attack per month and 12.0±5.3/15.0±4.6&25.6±5.4/20.9±5.5mmHg had reported where frequency of attack seen 11-20 times in a month with p value of 0.007, 0.002 and 0.003.

The difference of blood pressure from to standing position and diastolic blood pressure to hand grip test was statical significant (p < 0.05) with frequency of disease, above data shows that the fall in systolic and raise in diastolic blood pressure in greater frequency of seizure attack per month.

[Table 8] show that the heart rate has negative person's correlation between the heart rate and R-R interval of deep breathing/ EI ratio (r=-0.188**, p=0.008). Moreover, the heart rate was negatively correlated (r=-0.277**, p=0.000) with R-R interval during Valsalva maneuver.Furthermore, the heart rate was also negatively correlated with R-R interval of 30:15 standing ratio ((r=-0.163*, p=0.021)

[Table 9] The heart was positively correlated with duration of disease and frequency of seizure attack (r=0.149*, p=0.042&r=0.002, p=0.951). Moreover, there was negative correlation obtained between heart rate and interictal durationwith correlation coefficient of r=-0.035, p=0.620.The correlation of heart was statically significant (p<0.05) with duration of disease.

[Table 10] The mean Heart rate during interictal period was positively correlated to orthostatic blood pressure response (difference of SBP and DBP from

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supine to standing) and handgrip test index (DBP just before hand grip release and prior to handgrip test started) with correlation coefficient value (r) of 0.789**, 0.767**and 0.727**. All them were highly significant (p<0.001).

Table 1: Cardiovascular autonomic function tests.

Parameters	Normal Range	Patients Range	Patients
Heart Rate (beats/min)	60-100	46-125	80.52±17.59
E/I ratio	>1.07-1.23(<10 beats/min)	1.02-1.23	1.16±0.07
VM ratio	>1.45(<1.25)	0.78-2	1.30±0.18
30:15 standing ratio	1.10-1.15 (<1.03)	1-1.3	1.09±0.06
SBP/DBP in lying position (mmHg)	120/80 mmHg	100-148/60-98	125.4±10.8/80.6±7.43
SBP/DBP in Standing position (mmHg)	<120/>80 mmHg	96-132/66-120	114.8±7.1/93.3±11.48
Diff. SBP/DBP Supine to standing (mmHg)	SBP Fall > 20/ DBP raise<10mmHg (↓SBP<20 and ↓DBP <10mmHg-Sympathetic insufficiency)	↓2-20/↑4-22	↓12.5±4.75/↑13.4±4.7
SBP/DBP in strain(mmHg)	>140/>100 mmHg	110-180/74-122	150.5±14.4/100.35±10.6
SBP/DBP just before hand grip strain(mmHg)	120/80 mmHg	100-148/62-98	127.7±10.2/82.13±6.79
Diff. of SBP in HGT	↑>20mmHg	10-32	22.86±4.88
Diff. of DBP in HGT (mmHg)	↑>15mmHg (↑DBP <10mmHg, Sympathetic insufficiency)	8-28	18.77±3.5

Table 2: Heart rate in patients of seizure and epilepsy.

Heart Rate (HR)	Total
below 60 beats/min (Bradycardia)	31(15%)
60 to 100 beats/min (Normal)	150(75%)
above 100 beats/min (Tachycardia)	19(10%)
Total	200

Table 3: Cardiovascular Parasympathetic function test in both the genders.

Gender	Female	Male	P Value
E/Iratio	1.16±0.07	1.14±0.05	0.573
VMratio	1.30±0.19	1.28±0.18	0.987
Heart rate Response to Standing (30:15 ratio)	1.09±0.06	1.07±0.04	0.399
Difference of SBP from supine to standing (mmHg)	10.8±4.4	10.0±4.4	0.214
Difference of DBP from supine to standing (mmHg)	13.0±4.2	12.2±4.5	0.227
Difference of SBP in hand grip test (mmHg)	23.1±5.0	22.5±4.9	0.397
Difference of DBP in hand grip test (mmHg)	18.7±4.8	17.9±4.6	0.222

Table 4: Parasympathetic variables in different age groups

Age wise distribution	18-25 Year (Group I)	26-35 Year (Group II)	36-45 Year (Group III)	46-55 Year (Group IV)	>55 Year (Group V)	P Value
E/I ratio	1.16±0.07	1.14±0.07	1.15±0.07	1.17±0.06	1.19±0.04	0.092
VM ratio	1.30±0.18	1.26±0.16	1.29±0.20	1.27±0.20	1.41±0.17	0.039*
30:15 standing ratio	1.09±0.06	1.08±0.07	1.08±0.06	1.09±0.08	1.12±0.05	0.32
Difference of SBP from supine to standing (mmHg)	9.9±4.2	11.3±4.3	9.9±4.9	11.4±4.8	8.7±3.9	0.119
Difference of DBP from supine to standing (mmHg)	12.1±4.0	13.3±4.2	12.9±4.8	13.5±5.0	10.4±3.9	0.083
Difference of SBP in hand grip test (mmHg)	22.5±4.9	23.4±5.0	22.6±5.3	24.0±4.7	21.1±4.3	0.333
Difference of DBP in hand grip test (mmHg)	18.2±4.9	18.9±4.3	17.4±5.0	18.8±4.5	17.1±4.6	0.522

Table 5: Parasympathetic function test in different types of seizure and epilepsy.

Diagnosis	EP	GME	GTCS	SD	P Value
HR beats/min	81.35±20.44	89.48±22.34	80.37±17.31	78.67±15.85	0.145
E/I ratio	1.09±0.06	1.11±0.07	1.16±0.07	1.19±0.05	<0.001**
VM ratio	1.09±0.09	1.16±0.11	1.29±0.15	1.37±0.18	<0.001**
30:15 standing ratio	1.01±0.02	1.05±0.06	1.09±0.06	1.11±0.05	<0.001**
Difference of SBP from supine to standing (mmHg)	11.7±5.1	12.9±5.7	10.4±4.4	9.5±3.8	0.014
Difference of DBP from supine to standing (mmHg)	14.0±5.7	15.2±5.6	12.7±4.1	11.6±3.7	0.006
Difference of SBP in hand grip test (mmHg)	24.8±6.8	25.4±6.9	22.9±4.8	21.8±3.8	0.01
Difference of DBP in hand grip test (mmHg)	19.0±4.1	20.2±3.1	18.1±3.2	17.8±3.8	0.022

**= Highly significant p value<0.001

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Table 6: Parasympathetic variables with duration of disease.

Duration of disease	within a month	1-12 Month	24-60 month	72-120 Month	132-240 month	>240 Month	By Birth	P Value
HR beats/min	76.69±15.04	79.23±14.31	78.03±17.15	79.48±20.20	89.35±20.42	80.28±24.39	93.85±17.18	0.011*
E/I ratio	1.20±0.04	1.19±0.06	1.16±0.07	1.13±0.07	1.11±0.07	1.13±0.05	1.11±0.07	<0.0**01
VM ratio	1.47±0.15	1.40±0.16	1.28±0.14	1.17±0.07	1.12±0.11	1.13±0.02	1.13±0.05	<0.00**1
30:15 standing ratio	1.12±0.05	1.11±0.06	1.11±0.06	1.04±0.05	1.05±0.05	1.02±0.02	1.02±0.01	<0.00**1
Difference of SBP from supine to standing (mmHg)	8.4±2.8	8.6±3.4	10.4±4.0	10.8±5.4	12.9±5.1	13.3±6.4	14.7±4.1	<0.001
Difference of DBP from supine to standing (mmHg)	10.5±2.5	10.7±3.1	12.5±3.9	13.3±5.0	15.7±5.0	16.0±5.3	17.1±4.3	<0.001
Difference of SBP in hand grip test (mmHg)	21.0±3.2	22.2±3.8	21.9±4.1	22.6±5.9	26.1±6.4	29.3±1.2	27.0±5.9	<0.001
Difference of DBP in hand grip test (mmHg)	17.1±3.4	18.6±3.2	17.4±4.5	17.1±5.7	20.7±6.2	22.0±0.01	21.3±5.8	0.003

Table 7: Parasympathetic autonomic function test with frequency of seizure attack.

Frequency of attack/month	1st time	1-2/ Month	3-5/ Month	6-10/ Month	11-20/ Month	P Value
HR beats/min	77.91±15.93	85.63±17.78	74.55±17.16	79.65±14.11	83.51±16.85	0.003*
E/I ratio	1.19±0.04	1.15±0.07	1.16±0.07	1.16±0.06	1.16±0.06	0.042*
VM ratio	1.46±0.16	1.26±0.17	1.28±0.15	1.38±0.21	1.17±0.16	<0.001**
30:15 Standing ratio	1.12±0.05	1.08±0.07	1.09±0.06	1.10±0.06	1.05±0.06	0.004*
Difference of SBP from supine to standing (mmHg)	8.6±2.7	11.4±4.3	9.4±4.7	10.0±4.6	12.0	0.007
Difference of DBP from supine to standing (mmHg)	10.6±2.5	13.5±4.3	11.9±4.5	12.0±4.6	15.0	0.002
Difference of SBP in hand grip test (mmHg)	21.4±3.2	23.8±5.0	21.4±5.1	23.3±3.8	25.6	0.003
Difference of DBP in hand grip test (mmHg)	17.6±3.4	19.1±4.3	16.6±5.2	19.0±4.0	20.9	0.003

*= Significant p value <0.05, **= Highly significant p value<0.001

Table 8: Correlation of Heart rate and cardiovascular parasympathetic test variables.

		EIratio	VMratio	30: 15 standing Ratio
Heart Rate	Pearson Correlation	-0.188**	-0.277**	-0.163*
	Significance (2-tailed)	0.008	0.000	0.021

Table 9: Correlation of cardiac activity to clinical variables.

		Frequency of Seizure/ month	Duration Disease	Interictal Duration (number of Days from Last Attack)
Heart Rate	Pearson Correlation	0.004	0.149*	-0.035
	Sig. (2-tailed)	0.951	0.042	0.620

Table 10: Correlation of heart rate with blood pressure response.

		Difference of SBP from supine to standing (mmHg)	Difference of DBP from supine to standing (mmHg)	Difference of SBP just before hand grip release andprior to handgrip test started (mmHg)	Difference of DBP just before hand grip release andprior to handgrip test started (mmHg)
Heart Rate	Pearson Correlation	0.789**	0.767**	0.692**	0.727**
	pSig. (2-tailed)	0.000	0.000	0.000	0.000

DISCUSSION

Present study shows variation in heart rate such as bradycardia (31 patients,15%), normal (150 patients,75%) &tachycardia (19 patients,10%)) in patients of seizure and epilepsy.This may be due to alternative neural activation of right and left hemisphere in patients. In similarity of our findings this Fauchier L et al. (2000) reported increasedanddecreased instances of heart rate in patients of seizure.An increased heart rate show occurrence of serious ECG abnormalities.[10]

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StudyofWittling et al. (1998) is consistent with present study, they obtained that the right and left cerebral hemispheres activation contributes differently for cardiovascular changes. The left hemisphere predominantly modulates cardiac parasympathetic tone, by increasing its activity, and consequently provokes bradycardia, while the right hemisphere predominantly modulates cardiac sympathetic tone, by increasing its activity, and accordingly causes tachycardia. These activities were modulated by vasovagal stimulation and inhibition.[11,12]

Similarly, another study of Oppenheimer S.M. et al. (1992)also determined that the electrical stimulation of the insular cortex is responsible for cardiovascular changes. They reported that bradycardia was observed during left insular stimulation, while tachycardia occurred during right insular stimulation. Furthermore, neuroimaging studies, animal studies and clinical observations propose a hemispheric lateralization of parasympathetic or sympathetic cardiovascular control.[13,14]

In present study,the mean value of heart rate and parasympathetic tests in patients was obtained with in normal limits (HR;80.52±17.59 beats/mins, E/I ratio;1.16±0.07, VM ratio;1.30±0.18and 30:15 standing ratio;1.09±0.06). In contrast to our findings Shaker K.K. et al. (2021) reported significantly lower values of R–R interval in deep breathing, Valsalva maneuver and active standing in patients of epilepsyin comparison to control ($p = 0.012$; $p < 0.01$; and $p = 0.001$, respectively). They obtained abnormal autonomic (sympathetic and parasympathetic) regulatory functions in epilepsy (TLE and IGE)patients, suggested that epilepsy may alter the autonomic functions.[9]

In contrary, of present study Ansakorpi H et al. (2000) also reported the Heart-rate (HR) variation during normal breathing ($p = 0.006$) and tilting ($p=0.043$) were lower in patients with refractory TLE than controls. Interictal autonomic dysfunction was more evident in patients of refractory epilepsy. Harnod T et al. (2009) was identified that patients with frontal lobe epilepsy have shorter interictal heart rate intervals and faster heart rates, which postulate might be due to lower parasympathetic or vagal regulation of autonomic cardiac activity.[6,15]

In present study cardiovascular autonomic function test variables (E/I ratio, VM ratio, 30:15 standing ratio and blood pressure responses) were in-significantly ($p>0.05$) differ in both the genders and with various age groups of patients (Mukherjeea S. et al. (2009).[8]

In present study cardiovascular parasympathetic function test variables(E/I, VM and 30:15 standing ratio) were significantly ($p<0.001$) altered in different types of epilepsy and seizure.They were diminished in patients of epilepsy especially recurrent GME. In similar aspect of our results Kilvilinen R et al. (1990) reported hypofunction of parasympathetic test variables in patients of progressive myoclonus epilepsy, they alsoreported cardiovascular dysfunction in epilepsy patients.[16]

Similarly, Mukherjee S et al. (2009)obtained elevated heart rate in patients of Idopathetic Epilepsy (IE) in comparison of well controlled epilepsy (WcE) patients (85.36± 16.95, 81.43 ±12.65(bpm) $p=0.560$). They were also reported lower E:I ratio (in deep breathing test 1.29± 0.16 vs. 1.43± 0.21, $p=0.008$), Valsalva maneuverratio (VR) 1.93± 0.43 1.87± 0.46 $p=0.890$ and standing 30:15ratio (1.22± 0.36 1.11 ± 0.08$p=0.686$) in IE patients. In patients of IE, they observed a higher vasomotor tone, higher sympathetic tone, lower parasympathetic tone, lower parasympathetic reactivity and higher dysautonomia (chi square 165.0, $p<0.001$). It may lead alteration in cardiovascular autonomic regulation, which might be a predisposing factor for sudden unexpected death due to epilepsy (SUDEP). They also, determined that subjects with generalized epilepsies have more severe autonomic dysfunctions.[8]

In contrast to present study Evrengul H et al. (2005)found autonomic dysregulation and increase risk of SUDEP in patients GTCS, may be due extensive neural activation of frontal lobe foci spread to other brain regions of brain by GTCS. Which result to dysregulation of autonomic system in patients.[17]

In present study parasympathetic activity was significantly ($p<0.001$, <0.05) altered with duration of disease and frequency of attack. TheE/I, VM and 30:15 standing ratiowere reduced in patients with longer duration of disease and higher frequency of attacks. Our results are consistent withresults of Opherk C et al. (2000), who obtained significant ECG abnormalities in parasympathetic functional activity with longer duration of disease and higher number seizures attacks per monthinthe patients of generalized seizures.[18,19]

Finding of present are supported by Naritoku DK et al. (2003), who determined that repetition of seizures led to long-term abnormalities in the autonomic systems. By the same token, they reported that the autonomic dysfunction becomes more marked during the postictal and interictal period. Additionally, they also obtained that each seizure caused a sudden and temporary impairment in the autonomic functions, which reduce vasovagal control to CNS with longer duration of seizure activity.[20]

Alteration of parasympathetic parameters in present study consistent with Wasterlain et al. (1993)who described the changes during the interictal period might be related to chronic structural changes in autonomic centers, which continuously stimulated or inhibited by repetitive seizures. Along him Verrier RL et al. (2020) found that the repeated rises in catecholamines level and hypoxemia during chronic epilepsy might be causes the injury to heart and coronary vasculature (resulting,to dysfunction of electrical and mechanical activity).[21,22]

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Similarly, Schraeder PL et al. (1989) reportedthat the autonomic dysfunction during ictal or interictal periods in epileptic seizures patients associated with the effect of epileptic discharges on limbic structures, amygdala and peri-amygdaloid piriform cortex in particularmanner.[23]

In patients of present study faster heart rates or lower heart rate intervals correspond to lower parasympathetic activity rather than higher sympathetic drive.

Our study shows that parasympathetic activity maintained by neurons of vagus nerve, brainstem nucleus of vagus i.e. nucleus tractus solitarii (NTS) and dorsal motor nucleus and from releases of neurotransmitters like acetylcholine, GABA, and glutamate, which activate vagal neurons. In present study neuronal discharges at level of amygdala, hippocampus, hypothalamus, prefrontal cortex and anterior cingulate cortex by seizure patients may cause activation of vagal inhibitory neurons by alternating the brainstem nuclei activity, decrease the release of GABA and acetylcholine and increase the excitation of glutamate release from neurons. Inhibition of vagal discharge might be responsible for decrease in parasympathetic test variables and increase in heart in patients rather than higher sympathetic drive. Decrease in parasympathetic activity increase the risk of cardiovascular complications like cardiac tachyarrthymia and sudden unexpected death (SUDEP) in epilepsy patients (Monte CP et al. (2007)).PerssonH et al. (2005)also found decreased parasympathetic and increased sympathetic drive in patients of refractory epilepsy.[24,25]

In patients of present study, the mean differenceof diastolic blood pressure from lying to standing position was higher from normal. Our results are similar with results of Shaker K. K. et al. (2021), whoobtained significant ($p < 0.001$) elevation in blood pressure with people of epilepsy (PwE) from supine to standing position in comparison to controls.[9]

Present study shows that the difference of supine to standing systolic and diastolic blood pressure was significantly ($p<0.05$) altered in various types of seizure and epilepsy, higher in patients with GME (↓SBP; 12.9±5.7mmHg, ↑DBP; 15.2±5.6 mmHg).This may be due to either baroreceptor abnormalities or interference of seizure activity on central neurons (involved in baroreceptor modulation)by continuous activation of vasomotor neurons through neuronal discharge from recurrent GME patients.In support of our findingsMukherjee S et al.(2009) reported significant increase in diastolic BP from supine to standing position in epilepsy patients.They also obtained higher baseline BP in patients of idiopathic epilepsy without any concomitant changes in HR, signifying a higher vasomotor tone.[8]

Similarly, Kanter et al. (1995) determined that the seizure-induced activation of central neurons by involving the baroreflex modulation. Baroreflex sensitivity was seen to be lower in refractory TLE subjects and improve after resective surgery (Hilz et al., 2002).[26,27]

Finding of present study are supported by Massetani R et al. (1997), who stated that the interictal R–R interval and BP changes with epilepsy (PwE) indicate ANS (parasympathetic and sympathetic) dysregulation. They also reported that the epilepsy-related cardiac manifestationsdenote an inter relationship between the brain and heart in PwEmostly occursictally, but also reflects in the interictal period of various types of epilepsy (TLE & IGE).[28]

In present study the difference of diastolic blood pressure in hand grip test was significantly ($p<0.05$) altered in various types of seizure and epilepsy, increased in patients of recurrent generalised epilepsy may be due increased sympathetic activity. In similar aspect of our findings of this Vaseghiet al. (2008) reported interictal that the recurrent seizures on a chronic basis might increase sympathetic tone interictally and affect HR or BP during a resting state or in hang grip test. A state of chronically heightened sympathetic tone occurs in patients at high risk for sudden cardiac death (SUPD). Along him Umana et al. (2003) also reported that chronic tachycardia can cause cardiomyopathy and sudden cardiac death in patients of epilepsy.[29,30]

Our Results are consistent with results of Shobha N et al. (2007), who obtained significantly elevated systolic blood pressures (116.3±9.83 patient group versus 90.3±21.82 control group) to perform the cardiovascular reflex tests in fourteen patients with refractory seizures. They reportedless rise of systolic and diastolic blood pressures toorthostatic and isometric handgrip testin epilepsy patients ($p=0.01$). While, in contrastto present study there was no significant difference in diastolic blood pressures found between the patient and control group. The tests of parasympathetic activity i.e., Valsalva ratio and deep breathing ratio, had not shown any difference among patients and control subjects. They also determine reduction of sympathetic and parasympathetic modulation in patients of partial refractory epilepsy.[31]

In present study the difference diastolic blood pressure to hand grip test was significantly ($p<0.05$) altered with duration of disease and frequency of seizure. This increase in difference of diastolic blood pressure to hand grip test among patients was noticed with longer duration of disease and higher frequency of disease per month. Our findings are similar with findings of Shaker K.K. et al. (2021) study, who reportedsignificant ($p = 0.001$) increased in DBP of isometric hand grip test with duration of disease and greater number of attacks in epilepsy patients. Along him Sevcencu C et al. (2010) describedthat the repeated epileptogenic insults arising in the CANs may responsible for gradual interictal autonomic changes.[9,32]

Similarly, Holst AG et al. (2013) reported that the young adults with epilepsy had a 27fold higher risk

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of sudden unexplained death with increasing seizure frequency, seizure clustering (many define seizure clusters as > 3 seizures over 24 h since the average interictal period is ≤ 8 h) and time since epilepsy diagnosis, which remained elevated at 16 times higher risk even after adjusting for comorbidities associated with epilepsy. This risk may be modifiable as patients with seizure clusters and greater frequency. Who subsequently had better seizure control did not have an increased risk of death. Seizure control strongly influenced SUDEP risk in patients. Adult patients with childhood onset epilepsy with poor seizure control had a 5-fold increased risk of SUDEP. However, the relationship between seizure frequency, seizure clusters and SUDEP is understood.[33]

In contrast to present study Ronkainen E et al. (2005) found that there was no relationship between the cardiovascular autonomic functions and the severity of seizure attacks. Along him Ansakorpi Het al. (2000) previously reported that the neither the duration of epilepsy nor frequency of seizure correlated with the autonomic reflex in patients of temporal epilepsy.[6,34]

Normally, change in blood pressure senses by baroreceptorspresentonwalls of carotid sinus, aortic arch andvascular beds transmit afferent signals (by glossopharyngeal nerve (CN IX) and vagus nerve (CN X)) to brainstem and hypothalamus of central nervous system including nucleus tractus solitarii and ventromedial nucleus, they modulate the response by stimulation and inhibition of efferent vagus and Sympathetic nerves.

Our study explained the main regulatory loop for short-term BP control is termed of baroreflex. Baroreceptors maintain HR and SV by modulating sympathetic and parasympathetic system activity, whereas TPR is predominantly set by the sympathetic activity. If BP drops, for instance in the orthostatic reaction or in the second phase of a Valsalva maneuver, the firing rate of the baroreceptor afferents to the NTS decreases, which will in turn lead to a disinhibition of cardio-acceleratory neurons in the VLM and inhibition of cardio-inhibitory neurons in the NA and DVN, which directly and indirectly increases the HR, SV and TPR to re-set the drop of BP. If BP rises, for instance during intense muscular effort or the last phase of a Valsalva maneuver, the firing rate of the baroreceptor afferents to the NTS increases, which will in turn inhibit activity of cardio-acceleratory neurons in the VLM and their projections to the IML, which innervate the arterial blood vessels and in turn enhance activity of cardio inhibitory neurons in the NA and DVN thereby decreasing HR, SV and TPR to maintain the raised BP (Nass RD et al. (2019).[35]

Diencephalic connections of the NTS include thalamic nuclei as well as the hypothalamus and its endocrine regulatory centers. Among the telencephalic connections of NTS, the amygdalar-hippocampal complex, insular cortex, anterior cingulate gyrus and medial prefrontal area are involved. These supratentorial centers regulate the "desired" levels of sympathetic and parasympathetic output according to behavioral tasks and emotional states by adjusting a neural set point of BP.

In patients of present study during seizure attack vasodilatory blood pressure surge increases the blood pressure may be due increased in sympathetic tone by baroreflex mechanism, it sending signals to the NTS of brainstem which modulate the response by inhibiting sympathetic output and increasing parasympathetic activity through stimulation of vagus nerve (slows the heart rate) and inhibition of sympathetic nerve, which finally reduced sympathetic tone decreases vascular resistance and lowering blood pressure.

When this normal regulatory mechanism of baroreflex was disturb in patients might be sustained in interictal period due to widespread uncontrol neuronal excitation, it causes abnormal increase in blood pressure by enhancing the sympathetic activity overrides baroreflex-mediated vasodilation and increase in heart rate by impairing baroreflex-mediated decrease of vagal tone (or reduce in parasympathetic activity).

Similar to present study Nei M et al. (2016) reported that epilepsy is associated with interictal and ictal autonomic dysfunction. Seizures can immediately cause increases in blood pressure (BP) and heart rate (HR). However, it is unknown whether uncontrolled seizures, particularly when frequent, might chronically elevate the BP or HR. Additionally, it is unknown whether the interictal BP and HR is altered in individuals who are at risk for SUDEP, compared with other individuals with epilepsy. SUDEP often occurs in patients with highly refractory epilepsy. Such individuals might be at risk for a state of chronically heightened sympathetic tone, which might affect the HR and BP interictally. They compare the resting awake interictal HR and BP in individuals who subsequently died due to SUDEP and compared these to HR and BP in two control epilepsy groups (refractory and controlled). While the overall HR and BP are similar between groups, there is a trend toward a higher diastolic BP and more stable HR in individuals who subsequently died due to SUDEP, compared with epilepsy controls. These data suggest that there may be specific types of interictal autonomic dysfunction in individuals at risk for SUDEP. Such abnormalities might serve as markers for those at elevated risk for SUDEP.[19]

In contrast to our findings Devinsky et al. (1994), Isojarvi et al. (1998),Ansakorpi et al. (2000) and Dutschetal. (2006) identified the autonomic alteration in patients with epilepsy. Devinskyetal.(1994) found abnormal blood pressure(BP) in patients with complex partial seizures, which indicates impaired baroreflex functions in epilepsy. Indeed, investigation of Dutschetal. (2006) reported that the baroreflex responses in patients with TLE showed decreased

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baroreflex sensitivity. This is consistent with observations of Isojarvietal.(1998) who found diminished BP responses to isometric work, Valsalva maneuver and deep breathing in patients with various types of epilepsy. Similarly, Ansakorpi et al.(2000) also reported decreased HRV during tilting in patients with TLE. Such autonomic alterations were mostly identified during the day of seizure attack and sometime in interictal period also.[6,36]

The overall, observation of present study shows increase in sympathetic activity by increase in diastolic blood of isometric hand grip test and decrease in parasympathetic test variables to patients of recurrent generalized myoclonic epilepsy. In support of this Rajesh K. Goit et al. (2016)reported significant increase in sympathetic and decrease in parasympathetic control in HRV to patients presented with epilepsy.[37]

Similarly, study El-Sayed HL et al. (2007) clinically assessed cardiac autonomic functions by include standardized clinical tests of cardiac autonomic functions and observe short-term changes in the cardiac cycle as a reflection of the sympathetic and parasympathetic integrity (HR response to deep breathing and standing, blood pressure response to standing or isometric hand grip test and HR response to standing). They found that there is generalized dysfunction in the integrity of sympathetic as well as parasympathetic pathways.[38]

In contrary, to present findingsBerilgen MS et al. (2004) found sympathetic dysfunction in patients with partial epilepsy and parasympathetic dysfunction in patients with primary generalized seizures by evaluating ANS function during interictal period.[39]

Present study shows a positive correlation between the heart rate, duration of disease and frequency of seizure,while interictal duration was negatively correlated with heart rate (HR). Only the duration of disease was significantly correlated with HR. In contrast to our results Asadollahi M et al. (2019)reported no significant correlation betweenECG alternations,duration of epilepsy and seizures frequency by using person's correlation test, except for QRS duration (P-value: 0.03, R: 0.27).[40]

Present study shows negative correlation between the heart rate and parasympathetic variables like EI (r=-0.188**, p=0.008), VM (r=-0.277**, p=0.000) and 30:15 standing ratio ((r=-0.163*, p=0.021). Moreover, the mean Heart rate during interictal period was positively correlated to orthostatic blood pressure response (difference of SBP and DBP from supine to standing) with correlation coefficient value (r) of 0.789** and 0.767**. All the correlation were statically significant ($p \leq 0.001$ & 0.05) shows increase in vasomotor tone or sympathetic activity in patients.In analogue to present findings Fariaa M T et al. (2020) obtained positively correlation between heart rate and DBP handgrip test index ($r=0.727$, $p < 0.05$) in patients of epilepsy.[41]

CONCLUSION

In different aspect of disease, the increase in overall heart rate and significantly decrease in E/I, VM, L/S ratio as compare normal values accomplished lower parasympathetic activity in patients, thehigher difference diastolic blood pressure in hand grip test also exhibits increased sympathetic activity.Current study suggested interictally altered/dysfunction cardiovascular autonomictestes seems to be related with duration of disease, frequency of seizure, abnormal EEG report and to the epilepsy itself rather than the type of seizuredue to imbalance between lower parasympathetic and higher sympathetic tone, which maybe predisposed at risk for SUDEP in further. Further studies are needed for the evaluation of preictal, ictal and interictal changes in cardiac functions for better evaluation of patients at risk of cardiac disorders.

Ethics approval and consent to participate:

Present study was hospital based descriptive epidemiological study Cross-Sectional in design conducted after approval from IRB, ethical committee and Research Board Rajasthan university (No.RNT/ACAD./IEC/2022/288, Dated on 13.09.2022. Subjects were recruited with written consent.

List of abbreviations: -SUDEP, ECG, HR, E/I ratio, VM ratio, BP, EP, GME, GTCS & SD.

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REFERENCES

1. Fisher R S, Van Emde Boas W, Blume W, Elger C, Genton P, Lee P. Epileptic seizures and epilepsy: Definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005;46:470-2.
2. Ali R, Connolly Ian D, Feroze Abdullah H, Awad Ahmed J, ChoudhriOmar A, GrantGerald A. "Epilepsy: A disruptive force in history". World Neurosurgery. 2016;90:685-90.
3. Gourie-Devi M. Epidermiology of neurological disorders in India. Review of background, Prevalence and incidence of epilepsy, stroke, Parkinson's disease and tremors. Neurol India. 2014;62(6):588-98.
4. Sureka RK, Sureka R. Prevalence of epilepsy in rural Rajasthan, India. A door-to-door Survey.J Assoc Physicians India. 2007;55:741-2.
5. Allers K, Essue B M , Hackett M L, Muhunthan J, Anderson C. S., Pickles K, Scheibe F,Jan S. The economic impact of epilepsy: a systematic review.BMC Neurol. 2015 Nov 25:15:245.
6. Ansakorpi H, Korpelainen JT, Suominen K, Tolonen U, My llyla VV, Isojarvi JIT. Interictal cardiovascular autonomic responses in patients with temporal lobe epilepsy. Epilepsia 2000;41:42–7.
7. Aneesh P, Mohan M, Verma CS. The study of interictal EEG patterns in different types of seizures. Int J Sci Res Pub. 2013;3(9):2250-3153.
8. Mukherjeea S, Tripathib M, Chandrac P.S., Yadav R, Choudhary N, Sagar R. et al. Cardiovascular autonomic functions in well-controlled and intractable partial epilepsies. Epilepsy Research. 2009;85: 261—269.

ISSN(O):2687-5365;ISSN(P):2753-6556

9. Kanar K. Shaker, Akram M. Al Mahdawi and Farqad B. Hamdan. Interictal autonomic dysfunction in patients with epilepsy. Egypt J Neurol Psychiatry Neurosurg. 2021;57:165.
10. Fauchier L, Babuty D, Cosnay P. Epilepsy, Brugada syndrome and the risk of sudden unexpected death. J Neurol.2000;247:643–434.
11. Wittling W., A. Block, S. Genzel, and E. Schweiger. Hemisphere asymmetry in parasympathetic control of the heart. Neuropsychologia. 1998;36:461–468.
12. Koseoglu E, Kucuk S, Arman F, andErsoy A.O. "Factors that affect interictal cardiovascular autonomic dysfunction in temporal lobe epilepsy: role of hippocampal sclerosis". Epilepsy and Behavior.2009;16(4):617–621.
13. OppenheimerS.M., Gelb A, Girvin J.P., and Hachinski V.C., "Cardiovascular effects of human insular cortex stimulation". Neurology.1992;42(9):1727–1732.
14. Critchley H.D.,Elliott R., Mathias C.J., and Dolan R.J"Neural activity relating to generation and representation of galvanic skin conductance responses: a functional magnetic resonance imaging study". The Journal of Neuroscience. 2000;20(8):3033–3040.
15. Harnod, Chery, Yang C.H., Yue-Loong Hsin, Pen-Jung Wang, Kun-Ruey Shieh, Terry B.J. Kuo.Heart rate variability in patients with frontal lobe epilepsy. Seizure.2009;18 21–25.
16. Kilvilinen R, Keranen T, Mustonen J, Liinsimies E, Riekkinen PJ. Autonomic nervous system function in Baltic myoclonus epilepsy. E1~ilepsy Rex. l990;5:251-4.
17. Evrengul H, Tanriverdi H, Dursunoglu D, Kaftan A, Kuru O, Unlu U, et al. Time and frequency domain analyses of heart rate variability in patients with epilepsy. Epilepsy Res.2005;63:131–9.
18. Opherk C, Coromilas J, Hirsch LJ. Heart rate and EKG changes in 102 seizures: analysis of influencing factors. Neurology 2001; 56(l3):47.
19. Nei M, Ho RT, Sperling MR. EKG abnormalities during partial seizures in refractory epilepsy. Epilepsia 2000;41:542–8.
20. Naritoku DK, Casebeer DJ, Darbin O. Effects of seizure repetition on postictal and interictal neurocardiac regulation in the rat. Epilepsia 2003;44: 912–6.
21. Wasterlain, C. G., D. G. Fujikawa, L. Penix, and R. Sankar. 1993. Pathophysiological mechanisms of brain damage from status epilepticus. Epilepsia 34(Suppl. 1): S37–S53.
22. Verrier RL, Pang TD, Nearing BD, Schachter SC. The epileptic heart: concept and clinical evidence. Epilepsy Behav. 2020;105:106946.
23. Schraeder PL, Lathers CM. Paroxysmal autonomic dysfunction, epileptogenic activity and sudden death. Epilepsy Res.1989;3:55–62.
24. Monte CP, Arends JB, Tan IY, Aldenkamp AP, Limburg M, de Krom MC. Sudden unexpected death in epilepsy patients: risk factors. A systematic review. Seizure.2007;16:1–7.
25. PerssonH,KumlienE,EricsonM,TomsonT. Preoperative heart rate variability in relation to surgery outcome in refractory epilepsy. Neurology. 2005;65: 1021–5.
26. Kanter R.K., Strauss J.A., Sauro M. D. Seizure-induced c-fos expression in rat medulla oblongata is not dependent on associated elevation of blood pressure. Neurosci. Lett. 1995;194: 201—204.
27. Hilz M.J., Devinsky O., Doyle W., Mauerer A., DütschM. Decrease of sympathetic cardiovascular modulation after temporal lobe epilepsy surgery. Brain.2002;25 (5):985—995.
28. Massetani R, Strata G, Galli R, Gori S, Gneri C, Limbruno U, et al. Alteration of cardiac function in patients with temporal lobe epilepsy: different roles of EEG–ECG monitoring and spectral analysis of RR variability. Epilepsia. 1997;38:363–9.
29. Umana E.Solares CA, Alpert MA. Tachycardia-induced cardiomyopathy.Am. J. Med.2003;114(1):51-55.
30. Vaseghi M, Shivkumar K.The role of the autonomic nervous system in sudden cardiac deathProg. CardiovascDis.2008;50(6):404–419.
31. N Shobha, P Satishchandra, TN Sathyaprabha, K Udupa. A study of interictal cardiac autonomic functions in patients with refractory complex partial epilepsy secondary to medial temporal lobe pathology: Before and after surgery. Neurology Asia. 2007;12(1):69–70.
32. Sevcencu C, Struijk JJ. Autonomic alterations and cardiac changes in epilepsy. Epilepsia. 2010;51(5):725–37.
33. Holst AG, Winkel BG, Risgaard B, Nielsen JB, Rasmussen PV, Haunsø S, et al. Epilepsy and risk of death and sudden unexpected death in the young: a nationwide study. Epilepsia.2013.54:1613–20.
34. Ronkainen E, Ansakorpi H, Huikuri HV, Myllyla VV, Iso jarvi JI, Korpelainen JT. Suppressed circadian heart rate dynamics in temporal lobe epilepsy. J NeurolNeurosurg Psychiatry.2005;76:1382–6.
35. Nass RD, Hampel KG, Elger CE and Surges R Blood Pressure in Seizures and Epilepsy. Front. Neurol.2019;10:501.
36. Nei M, Mintzer S, Skidmore C,Sperling M. R,Reginald T. Ho .Heart rate and blood pressure in sudden unexpected death in epilepsy (SUDEP).Epilepsy Research.2016;122:44-46.
37. Rajesh K. Goit, Santosh K. Jha & Bhawana N. Pant Alteration of cardiac autonomic function in patients with newly diagnosed epilepsy. Physiol Rep.2016;4(11):e12826.
38. El-Sayed HL, Kotby AA, Tomoum HY, El-Hadidi ES, El Behery SE, El-Ganzory AM. Non-invasive assessment of cardioregulatory autonomic functions in children with epilepsy. Acta Neurol Scand. 2007;115: 377–384.
39. Berilgen MS, SariT, BulutS, MungenB. Effects of epilepsy on autonomic nervous system and respiratory function tests. Epilepsy Behav.2004;5:513–6.
40. Asadollahi M, Shahidi M, Ramezani M, SheibaniM.Interictal electrocardiographic alternations in patients with drug-resistant epilepsy.Seizure.2019;69:7-10.
41. Fariaa M T, Regob R, Rochab H, Sáb F, Farinhac R, Oliveiraa A, BaratadP,Alvesb D. et al. cTnI, BNP and CRP profiling after seizures in patients with drug-resistant epilepsy. Seizure European Journal of epilepsy.2020;80:100-108.

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