Original article

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Study of cardiac autonomic function in drug-naïve, newly diagnosed epilepsy patients

Peter Mativo[1], Javad Anjum[2], Cauchy Pradhan[3], Talakad N. Sathyaprabha[2], Trichur R. Raju[2], Parthasarathy Satishchandra[3]

[1] Department of Medicine, Aga Khan University, Nairobi, Kenya
[2] Department of Neurophysiology
[3] Department of Neurology, National Institute of Mental Health and Neurosciences, Bangalore, India

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ABSTRACT – *Background*. Epilepsy is associated with ictal autonomic dysfunction which may extend into the inter-ictal period. Antiepileptic drugs have often been blamed for cardiac autonomic dysfunction in epilepsy patients. In this study we have investigated cardiac autonomic parameters in order to evaluate autonomic functions of drug-naïve epilepsy patients. *Method*. Twenty drug-naïve patients (15 males and 5 females) with epilepsy, and an equal number of age and gender matched controls, were evaluated for short-term resting heart rate variability and conventional cardiovascular autonomic measurements. *Results*. The mean age of patients was 29.30 ± 9.80 yrs (17-55 yrs), mean age at seizure onset was 19.70 ± 9.15 yrs (3-40 yrs) and mean length of time since last seizure was 5.60 ± 7.00 days (1-30 days). While there was no difference in the resting heart rate or conventional autonomic test parameters, time domain heart rate variability measurements showed a decreased percentage of R-R intervals of less than 50 ms and root mean square of R-R intervals in patients, when compared to controls. Frequency domain parameters showed a decreased total power (patients: 1,796.58 ± 1,052.45 ms^2; controls: 2,934.23 ± 1,767.06 ms^2, p = 0.008). Parameters indicative of decreased vagal tone, *i.e.* decreased high frequency power and increased low to high frequency ratio (patients: 1.69 ± 0.94; controls: 1.14 ± 0.64, p = 0.045), were observed among patients compared to controls. *Conclusion*. Subtle but definite cardiac autonomic dysfunction, especially in vagal tone, was identified in drug-naïve, new-onset epilepsy patients. Seizures can cause long-term and often progressive cardiac autonomic dysfunction which may be independent of concomitant antiepileptic drugs.

Key words: autonomic function tests, heart rate variability, drug-naïve, newly diagnosed epilepsy, SUDEP

Correspondence:
Dr P. Satishchandra
Professor of Neurology,
National Institute of Mental Health and NeuroSciences (NIMHANS),
Hosur road,
Bangalore, India 560 029
<dr.p.satishchandra@gmail.com>

Activation of the autonomic nervous system has been well documented in patients receiving electroconvulsive therapy (ECT) and in those with spontaneous symptomatic seizures during ictus (Brown *et al.*, 1953; Van Buren, 1958). Autonomic dysfunction has also been noted to extend well into the inter-ictal period and could be the only sign during this phase of clinical calm. Several studies have shown that the clinical hallmark of seizure onset

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is a decreased variability in the heart rate and decreased sympathetic tone resulting from autonomic activation (Nashef *et al.*, 1996; Novak *et al.*, 1999; Lai *et al.*, 2008). Autonomic dysfunction is more prominent in patients with refractory epilepsy as well as in long-standing and well controlled epilepsy. Possible mechanisms for this dysfunction include uncontrolled electrical stimulation and/or chronic functional changes in the related neuroanatomical regions of the brain (Ansakorpi *et al.*, 2002). We have previously demonstrated a significant inter-ictal autonomic dysfunction in patients with refractory epilepsy (Sathyaprabha *et al.*, 2006).

Sudden unexplained death in epilepsy (SUDEP) remains an important cause of mortality in refractory epilepsy (Nashef *et al.*, 1996). Although the exact mechanisms of SUDEP are presently unclear, autonomic dysfunction is said to play a significant role. Diehl and colleagues demonstrated an inter-ictal increase in the sympathetic modulation of cerebral blood flow velocities in epilepsy patients (Diehl *et al.*, 1997). Inter-ictal spikes seen in an electroencephalograph (EEG) might also suggest subclinical electrical seizures and thus ongoing autonomic activation. Autonomic dysfunction in epilepsy was previously attributed partly to the use and withdrawal of anticonvulsants, especially carbamazepine (Hennessy *et al.*, 2001). Administration of this drug has been shown to decrease heart rate variability and cause parasympathetic hypofunction. Studies by our group (Sathyaprabha *et al.*, 2006) and Berilgen *et al.* (2004) have shown no significant association between autonomic dysfunction and the use of anticonvulsants. Berilgen *et al.* (2004) have also suggested that autonomic changes are amenable to antiepileptic medication.

It has remained unclear, however, whether autonomic dysfunction evolves in new-onset, drug-naïve, epilepsy patients. One previous study evaluating cardiac autonomic parameters in drug-naïve patients using conventional autonomic tests did not show any dysfunction (Isojärvi *et al.*, 1998). Functional imaging studies in drug-naïve epilepsy patients have shown abnormal inter-ictal regional cortical blood flow in areas responsible for autonomic modulation (Joo *et al.*, 2008). We undertook this study of drug-naïve, newly diagnosed epilepsy patients to investigate whether epilepsy *per se* causes cardiovascular autonomic dysfunction and whether this dysfunction occurs at very early stages in the disease process. As well as conventional autonomic tests, sensitive techniques such as spectral changes in heart rate variability were used to assess cardiac autonomic function.

Patients and methods

This study was carried out at a university teaching hospital, a leading tertiary neuropsychiatric referral centre in Southern India. This study was approved by the institute ethical committee and written informed consent was obtained from each subject. Adult patients with untreated and newly diagnosed epilepsy were individually inducted into the study. Clinical seizure semiology and frequency were noted for each patient and inter-ictal EEG was performed to corroborate clinical diagnosis. Computerised tomography (CT) or magnetic resonance imaging (MRI) was performed for all patients to determine structural pathology. Patients who were clinically diagnosed as having idiopathic generalised tonic-clonic epilepsy with normal imaging (CT/MRI) were subjected to autonomic function tests. Patients who had a seizure during the previous 24-hour period were excluded. Age and gender matched healthy controls were chosen from amongst relatives of patients and hospital staff. Subjects with diabetes mellitus, endocrinological disorders, cardiopulmonary diseases, Parkinson's disease or a history of substance abuse were excluded. Patients with structural abnormalities based on imaging were also excluded. Female subjects who were either pregnant or lactating were also excluded from the study.

Cardiovascular autonomic function tests

The patients were subjected to a battery of standardised Autonomic Function Tests (AFT) for the assessment of cardiac autonomic functions. For female subjects, the autonomic tests were done during the proliferative phase of their menstrual cycle. Electrocardiogram and blood pressure were recorded during normal breathing and after rest in supine position for 30 min.

The ECG signal was acquired digitally at 256 samples per second. Consecutive RR intervals, defined as the time elapsing between two consecutive R waves in the electrocardiogram measured from the ECG for a period of 1 min, and standard deviation (SD) of the intervals were used as baseline variables. The procedure has been described in detail in previous publications (Sathyaprabha *et al.*, 2006, 2008).

The autonomic parameters measured included:

– heart rate (HR) parameters:
  - deep breathing ratio (beats/min),
  - Valsalva ratio,
  - min:max ratio;

– blood pressure (BP) measurements:
  - isometric ΔDBP (mmHg),
  - standing ΔSBP (mmHg).

Heart rate variability

A five-minute error-free Lead II electrocardiogram was recorded for all individuals at rest and supine position under standard conditions. The raw ECG was converted into consecutive R-R intervals for analysis. Analysis was performed using HRV Analysis Software V1.1 (Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland).

The following parameters were chosen as per the recommendations of the European Society of Cardiology, 1996 (Camm and Malik, 1996).

– Time domain parameters:
- heart rate (beats/min),
- mean RR interval (ms),
- mean standard deviation of successive R-R intervals (RRSD) (ms),
- root mean square (square root of the mean squared) successive difference of intervals (RMSSD) (ms),
- number of interval differences of successive RR intervals greater than 50 ms (NN50). NN50 divided by the total number of NN intervals (pNN50).

– Spectral analysis for frequency domain parameters was performed using parametric spectrum analysis (auto-regressive modelling). The following parameters were measured:
- total power (TOTP) (ms^2),
- very low frequency absolute power (VLFP) (ms^2),
- low frequency absolute power (LFP) (ms^2),
- high frequency absolute power (HFP) (ms^2),
- low frequency absolute power expressed in normalised units (LFnu) (ms^2),
- high frequency absolute power expressed in normalised units (HFnu) (ms^2),
- LF/HF ratio.

Statistical analysis

All continuous variables were expressed as mean ± standard deviation. Comparison between patients and controls was carried out using the Mann-Whitney U test. Significance was set at $p < 0.05$.

Results

Of the 20 patients, none had a history of status epilepticus or concurrent drug use for other ailments. Imaging studies showed that these patients did not have any structural abnormalities. Demographic details of patients and healthy controls are given in *table 1*. The mean age of patients was 29.3 ± 9.8 yrs (17-55 yrs), mean age at seizure onset was 19.7 ± 9.2 yrs (3-40 yrs) and mean length of time since last seizure was 5.6 ± 7.0 days (1-30 days). The comparison of conventional cardiovascular reflex tests is presented in *table 2*. There was no statistically significant difference in conventional autonomic test parameters between patients and controls. The heart rate variability measurements from both groups are presented in *table 3*. Time domain heart rate variability measurements showed a significant decreased percentage of R-R intervals less than 50 ms and root mean square of R-R intervals in patients, when compared to controls. Frequency domain parameters showed decreased total and high frequency power in patients when compared to controls. Patients also had an increased low to high frequency ratio. When expressed in normalised units, patients demonstrated an increase in low frequency power and a trend towards a decrease in high frequency power.

Discussion

The patients' demographic data shows that while the mean age of patients was 29.30 years, the mean age at seizure onset was 19.70 years. This is unusual given that

Table 1. Demographic data.

	Patients (n = 20)	Controls (n = 20)
Age (years)	29.3 ± 9.8 (17-55)	28.8 ± 6.2 (20-44)
Sex (M:F)	15:5	15:5
Age at onset (years)	19.7 ± 9.2 (3-40)	NA
Duration of illness (months)	52.8 ± 70.1 (0.7-182.5)	NA
Seizure frequency (days)*	334.1 ± 609.4 (0-2185)	NA
Seizure free interval (days)	5.6 ± 6.99 (1-30)	NA

* Interval between first and second seizure; NA: not applicable.

Table 2. Conventional autonomic function tests.

Autonomic function test	Patients (n = 20)	Controls (n = 20)	P
Deep breathing ratio	22.95 ± 10.03	22.41 ± 6.43	0.657
Valsalva ratio	1.63 ± 0.33	1.45 ± 0.18	0.347
Max:min ratio	1.37 ± 0.19	1.38 ± 0.18	0.754
Isometric hand grip ΔDBP (mm Hg)	8.70 ± 5.59	11.45 ± 5.09	0.094
Standing ΔSBP (mm Hg)	6.20 ± 3.35	5.50 ± 1.79	0.415

SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 3. Time domain and frequency domain analysis of heart rate variability.

Parameter	Patients (n = 20)	Controls (n = 20)	P
Mean heart rate (beats/min)	75.93 ± 13.08	74.4 ± 8.2	0.375
RRSD (ms)	49.99 ± 25.49	39.7 ± 8.4	0.076
RMSSD (ms)	30.32 ± 9.67	35.0 ± 13.7	0.001
NN50	109.35 ± 172.79	47.4 ± 49.2	0.657
pNN50	9.77 ± 8.95	13.9 ± 14.3	< 0.001
TOTP (ms^2)	1,796.58 ± 1,052.45	2,934.23 ± 1,767.06	0.008
LFP (ms^2)	579.75 ± 418.99	863.62 ± 638.45	0.054
HFP (ms^2)	396.05 ± 248.61	935.54 ± 966.10	0.001
LFnu (ms^2)	55.04 ± 13.55	46.35 ± 12.79	0.045
HFnu (ms^2)	39.05 ± 12.94	46.95 ± 12.63	0.064
LF/HF	1.69 ± 0.94	1.14 ± 0.64	0.045

RRSD: standard deviation of R-R interval; RMSSD: root mean square successive difference of intervals; NN50: number of interval differences of successive RR intervals greater than 50 ms; pNN50: percentage of NN50; TOTP: total power; VLFP: very low frequency absolute power; LFP: low frequency absolute power; HFP: high frequency absolute power; LFnu: low frequency absolute power in normalised units; HFnu: high frequency absolute power in normalised units; LF/HF: low frequency to high frequency ratio.

a previous study has shown that the average delay from diagnosis to treatment in urban India was about 1.5 ± 4 years (Thomas, 2001). Our population was derived predominantly from rural India and socio-cultural practices may have lead to the longer delay in obtaining treatment. In most cases the age at seizure onset was a retrospective estimate based on clinical history. Patients might have avoided allopathic medical treatment since early episodes may have been unrecognised by caregivers. Duration of untreated epilepsy varies greatly even in western cohorts; in the study of Persson *et al.* (2007) four of 22 subjects experienced seizures without treatment for 10 years or more and nine for a period of one year or more. In order to take into account the large variation of duration of illness prior to diagnosis, we calculated seizure frequency as the duration between the first and second seizure. The 24-hour gap between the last seizure and autonomic tests excluded behavioural and post-ictal autonomic influences. The predominately male representation of our cohort was also probably due to prevailing socio-cultural factors.

Standardised autonomic tests did not reveal any differences between patients and controls. This finding is similar to that of a previous study by Isojärvi *et al.* (1998) who concluded that inter-ictal autonomic nervous system function in patients with untreated epilepsy was not significantly different from that of healthy control subjects, based on standardised cardiovascular reflex tests. However, in this study, heart rate variability parameters, which are more sensitive indicators, demonstrated a significant difference between patients and control subjects. Time domain parameters RMSSD and pNN50 correspond approximately to HFP which is considered to be a measure of vagal tone. This is based on the presumption that vagal (neural) modulation of HRV occurs at a faster rate than sympathetic (vascular) modulation (Camm and Malik, 1996). Using both time domain and frequency domain parameters, subtle cardiac autonomic dysfunction, especially in the vagal tone in drug-naïve, new-onset epilepsy patients, was identified. A previous study of HRV in newly diagnosed military recruits with epilepsy reported reduced HF, increased LF and an increased LF/HF ratio (Evrengül *et al.*, 2005). These findings were replicated in our study with frequency domain parameters showing decreased total power and high frequency power in patients when compared to controls. Patients also demonstrated an increased high frequency to low frequency ratio. When expressed in normalised units, patients demonstrated an increase in low frequency power and a trend towards decrease in high frequency power. Time domain heart rate variability measurements showed a decreased percentage of R-R intervals less than 50 ms and root mean square of R-R intervals in patients, when compared to controls.

In the similar study of Persson *et al.* (2007) no HRV abnormalities were identified in a cohort of 22 drug-naïve patients. This series consisted of patients with both complex partial seizures and generalised tonic-clonic seizures. While the dissimilar inclusion criteria may have contributed to the difference in findings between our study and that of Persson *et al.* (2007), the longer duration of unrecognised and thus untreated seizures in our study may also have contributed.

Activation of the autonomic nervous system is a well known ictal phenomenon in patients with epilepsy. This activation is known to extend well into the inter-ictal phase. Numerous studies have shown decreased heart rate variability and decreased sympathetic tone caused by autonomic activation (Nashef *et al.*, 1996; Novak *et al.*, 1999; Lai *et al.*, 2008). Almost all patients with

generalised tonic-clonic seizures have ictal autonomic changes and a third with partial seizures also develop autonomic dysfunction (Nouri and Balish, 2008). Seizures can cause long-term and often progressive cardiac autonomic dysfunction (Ansakorpi *et al.;* 2002, Sathyaprabha *et al.*, 2006). Autonomic dysfunction is more prominent in patients with refractory epilepsy and could be caused by uncontrolled electrical stimulation and chronic functional changes in the related neuroanatomical regions of the brain. SUDEP remains an important cause of mortality in refractory epilepsy. Several mechanisms for SUDEP have been proposed. Of these, parasympathetic dysfunction, leading to central apnoea, arrhythmias and cardiac failure is believed to play a crucial role (Nashef *et al.*, 1996). While the link between antiepileptic medication and autonomic dysfunction remains controversial, especially with regards to carbamazepine, Berilgen *et al.* (2004) have suggested that autonomic changes are amenable to antiepileptic medication and future studies should be aimed at demonstrating normalisation of cardiac parameters of patients with specific antiepileptic treatment. Hence, early assessment of autonomic dysfunction and further preventive strategies may be useful to avoid cases of SUDEP.

Conclusion

In this study we sought to investigate the presence of cardiovascular autonomic dysfunction using sensitive measurements, such as heart rate variability, in drug-naïve epilepsy patients with idiopathic generalised tonic-clonic epilepsy. Subtle cardiac autonomic dysfunction, especially in vagal tone, was identified in these patients. Since seizures are already known to cause long-term and often progressive cardiac autonomic dysfunction, early, comprehensive and aggressive management of epilepsy may stabilise any dysfunction and help prevent SUDEP. Future research should require longitudinal studies using larger cohorts of newly diagnosed, drug-naïve epileptic patients. □

Disclosure.
None of the authors has any conflict of interest or financial support to disclose.

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