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Heart rate variability in frontal lobe epilepsy: Association with SUDEP risk

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Objectives: Frontal lobe epilepsy (FLE) may impair autonomic heart rate modulation. Decreased heart rate variability (HRV) may enhance risk of sudden death. Our objective was to describe whole day and wakefulness/sleep HRV parameters from FLE patients in comparison with those of healthy controls and correlate HRV parameters to SUDEP-7 scores.

Methods: Ten patients with FLE and 15 healthy controls underwent a 24-hour electrocardiogram holter. The SUDEP-7 score was calculated for patients. Subgroups were identified according to active epilepsy, number of generalized seizures, cognitive deficit, medication load, and time-length of epilepsy. Time-domain SDNN, SDNNi, SDANN, rMSDD, and pNN50 and frequency-domain LF, HF, and LF/HF parameters were analyzed. Wilcoxon and Spearman correlation tests were used. A $P < .05$ was considered significant.

Results: Patients SDNN, SDNNi, rMSSD, and pNN50 were decreased in 24-hour recordings. Although a tendency for a protective effect of sleep was seen for both patients and controls, intragroup comparisons of sleeping/waking states revealed a significant increase in sleep rMSSD ($P = .046$) and pNN50 ($P = .041$) only for controls. All 24-hour time-domain parameters and LF were inversely and significantly correlated to SUDEP-7, particularly SDANN ($\rho = -0.896$, $P = .00019$), known to deteriorate with diminished physical activity and decreased in patients with more generalized seizures. Wakefulness parameters did not correlate to SUDEP-7, whereas correlations to sleep parameters were very strong, particularly with rMSSD ($\rho = -0.945$, $P = .00012$). Cognitive deficit was associated with decreased pNN50, sleep pNN50, and LH.

Conclusion: HRV is impaired in patients with FLE. Low HRV scores are associated with increased risk for SUDEP as measured by the SUDEP-7 score.

KEYWORDS

autonomic modulation, frontal lobe epilepsy, heart rate variability, sleep, SUDEP-7, wakefulness

1 | INTRODUCTION

Frequent generalized tonic-clonic seizures are a well-known risk factor for sudden unexpected death in epilepsy (SUDEP).[1,2] There is evidence that frequent tonic-clonic seizures are common in patients with frontal lobe epilepsy (FLE), placing them at risk for SUDEP.[3,4] Nevertheless, we lack predictive biomarkers for SUDEP in this population.[2,5,6] FLE is a common form of focal epilepsy characterized by recurrent, often brief seizures arising from the frontal lobes, occurring several times a day and frequently during sleep,[7,8] including motor, autonomic, behavioral, hypermotor, disperceptive, or tonic-clonic phenomenology.[3,7] Hughlings Jackson correlated the frontal lobe to autonomic functions in 1876.[9] The prefrontal cortex projects to the sympathetic and parasympathetic centers.[4,10,11] Voxel-based morphometry studies from patients at risk for SUDEP showed thinning of the mesial and orbitofrontal cortex.[12,13] No consistent rate of SUDEP for FLE has been established.

Heart rate variability (HRV) procedures measure the autonomic regulation of the sinus node.[14] Time-domain HRV parameters comprise long-term SDNN, SDNNi, and SDANN, translating both sympathetic and parasympathetic activities, and short-term rMSSD and pNN50, reflecting parasympathetic activity. Main frequency-domain parameters comprise high frequency (HF), measuring parasympathetic activity, and low frequency (LF), signaling sympathetic and parasympathetic influence. Higher HRV parameters mean good autonomic adaptability whereas lower HRV parameters may serve as biomarkers for risk of SUDEP. Lower HRV was firstly associated with worse prognosis in cardiac disease,[15-17] but strict normal values of HRV were not determined. As regards epilepsy, lower rMSSD has been associated with higher risk of SUPEP[6,18] and FLE, to higher heart rates and lower HF.[4] One study showed lower awake HRV or very high/low sleep to awake HRV ratios in patients having died of SUDEP.[19] Patients with SCN gene mutations showed worse autonomic function.[19] Autonomic dysfunction may thus be part of a brain disease causing epilepsy or both may derive from a shared biological susceptibility.[20] Given the relationship between the frontal lobe and the autonomic centers, we aimed to compare interictal parameters of HRV of FLE patients to those of a control group in a 24-hour electrocardiogram Holter and correlate them to the risk of SUDEP. In order to take circadian influences into account, long- and short-term time-domain parameters were analyzed in sleep and wakefulness.

2 | PATIENTS AND METHODS

This cross-sectional observational study is part of an ongoing research project aiming at evaluating consecutive patients from the outpatient Epilepsy Service approved by the Gaffrée e Guinle University Hospital Ethics Committee (Federal University of Rio de Janeiro State) under the number 56196316.9.0000.5258.

All patients were submitted to video-electroencephalogram recording and to magnetic resonance imaging to assist in diagnosis. Inclusion criteria were a diagnosis of FLE according to The International League Against Epilepsy,[21] a stable antiepileptic medication regimen for at least 6 months, age between 18 and 70 years and freedom of all comorbidities. Patients were classified as having active or inactive epilepsy. Active epilepsy was defined as persistency of focal seizures during the previous 3 months or at least one generalized seizure in the previous 6 months. Patients were evaluated for risk of SUDEP by means of the SUDEP-7, a seven question inventory with a scoring range from 0 to 12, where 12 represents the maximum risk of SUDEP.[18,22]

2.1 | Patients' selection

Patients were selected from the Epilepsy outpatient service of the Gaffrée e Guinle University Hospital from December 2017 to September 2018. Controls were recruited matching patients' age and gender distribution. All patients and controls provided written informed consent.

2.2 | Procedures

Patients and controls were submitted to a 24-hour EKG Holter recording using a 6-channel digital Holter with flash memory and a 512 Hz sampling rate (DMS-300 Digital Holter Recorder 3A, California, USA). HRV parameters were obtained using the Holter software version 11.0 (Cardioscan, DMS, USA). Volunteers were encouraged to keep their regular activities according to their sleep-wakefulness cycle and keep a diary where to register their activities, periods of sleep, medication use, and eventful symptoms. This was meant to eliminate periods of seizures from further analysis. Holter recordings were evaluated by ET, blinded to the patients' clinical data.

2.3 | Data analysis

Variables studied were age, gender, body mass index (BMI – kg/m^2), mean cardiac frequency, SDNN, SDNN index, SDANN, rMSSD, pNN50, LF, HF, LF/HF, the SUDEP-7 Inventory score and the existence of active or inactive epilepsy.

SDNN is defined as the standard deviation of all NN intervals, SDANN is the standard deviation of the averages of NN intervals in all 5 minutes segments of the recording, RMSSD is the square root of the mean of the sum of the squares of differences between adjacent NN intervals, and SDNN index is the mean of the standard deviations of all NN intervals for all 5 minutes segments of the recording. These are measured in milliseconds (ms). NN50 count is the number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording. The pNN50% is the NN50 count divided by the

total number of all NN intervals.[14] HF (high frequency) corresponds to a fluctuation of 0.15-0.4 Hz and LF (low frequency), to a 0.04-0.15 Hz fluctuation.[14] From knowledge on cardiac disease, SDANN <40 ms, SDNN <50 ms, rMSSD <15 ms, and pNN50 <1% were considered markers of worse prognosis.[15]

An initial analysis involved the comparison of HRV parameters between patient and control groups for the whole 24-hour recording. Further, parameters were evaluated for each group during sleep and wakefulness periods. A correlation analysis was performed between the SUDEP-7 Inventory scores and each HRV parameter. Active epilepsy and four items from the SUDEP-7 Inventory, namely intellectual disability, having had more than 3 tonic-clonic seizures during the previous year, current use of at least 3 antiepileptic medications, and duration of disease of more than 30 years were used for subgroups comparison.

Statistical analysis was performed using the R program version 3.3.3 and comprised descriptive statistics, data distribution analysis using the Shapiro-Wilk test, group comparisons using the Wilcoxon test and correlation analysis using the Spearman test. Spearman rho coefficients were considered either very strong (0.90-1.0), strong (0.70-0.89), moderate (0.50-0.69), weak (0.30-0.49), or negligible (<0.30). A significance level of 5% was adopted.

3 | RESULTS

From 384 consecutive patients seen during the recruitment period, 52 were diagnosed with FLE accordingly to the ILAE criteria (2017). From these, fifteen patients were excluded for having arterial hypertension, nine for having diabetes mellitus, seven for having hypothyroidism, ten for having depression (either treated or non-treated with antidepressive medication), and one for suffering from chronic renal failure. Thus, a final sample of ten patients was selected from which five were women (50%). Mean age was 35.1 years (SD = 10.66). Four patients were pharmacoresistant. Time since diagnosis varied from 1 to 47 years, mean time = 22.4 years (SD = 13.64). SUDEP-7 score ranged from 1 to 8, mean 4.8 (SD = 2.6). No patient reported seizures during the recording. Table 1 shows main patients' characteristics.

Initially, 18 age and gender-matched healthy individuals were selected among patients' relatives and HUGG working personnel for a control group. Three of them were excluded for not having completed the 24-hour Holter record. Our final control sample was composed of 15 individuals, nine being women (60%). Mean age was 35.6 years (SD = 12.61).

Body mass index was similar among patients and controls as shown in Table 2.

TABLE 1 Frontal lobe epilepsy patients

Patients	Gender	Age	Seizure control	Seizure types	EEG
1	M	26	No	Focal disperceptive Bilateral tonic clonic	Interictal: Sharp waves Fp1, F3, F7, Fp2. Ictal: Bilateral frontal and generalized spike and wave discharges with maximum amplitude on the right.
2	M	47	Yes	Focal left clonic facio-brachial Bilateral tonic clonic	Interictal: Bilateral frontal sharp waves F3, F7, F4, F8 with maximum amplitude on the left.
3	F	48	Yes	Focal emotional (anguish and fear); Bilateral tonic clonic	Interictal: Sharp waves F8 during sleep
4	M	22	Yes	Focal right clonic facio-brachial Bilateral tonic clonic	Interictal: Sharp wave F3
5	F	32	No	Focal disperceptive with hyperkinetic automatisms	Ictal: Continuous bilateral frontal sharp waves discharges during sleep
6	M	18	Yes	Bilateral tonic clonic	Interictal: Left frontal sharp waves Fp1, F3, F7; generalized 3-5 Hz sharp waves discharges. Left frontal polymorphic theta waves.
7	F	35	No	Focal disperceptive; Focal hyperkinetic.	Interictal: left frontal sharp waves F3, F7. Ictal: Muscular artifacts.
8	F	51	Yes	Focal atonic seizure of left arm Focal disperceptive Bilateral tonic clonic.	Normal
9	F	39	No	Focal disperceptive Focal right facial clonic Bilateral tonic clonic	Interictal: Left frontal sharp waves F3, less often parietal P3
10	M	34	Yes	Focal disperceptive Bilateral tonic clonic	Interictal: Right frontal sharp waves Fp2, F4

Two patients (1 and 8) had episodes of limited supraventricular tachycardia. One patient (9) presented an ST segment depression >1 mm and was investigated by the HUGG Cardiology team who discarded any structural cardiac or coronary disease. No supraventricular electrical instability or any sign of ischemic disease was found among volunteers of the control group. Parameters of bad prognosis were found as follows: One patient presented SDNN <50 ms (patient 9), two patients had rMSSD <15 ms (patients 1 and 8), and two patients (patients 1 and 8) and four controls showed pNN50 <1%. Patients 1, 7, 9, and 10 had active epilepsy. Patients 1, 2, and 9 had severe cognitive deficit. Patients 1, 9, and 10 had had at least 3 tonic-clonic seizures during the year previous to the holter recording. Patients 2, 8, and 10 had at least 30 years of epilepsy. Patients 7, 8, and 9 were under at least three antiepileptic medications.

As the ensemble of all HRV parameters was non-normally distributed, further analysis was performed using the Wilcoxon test. A primary analysis was made using the whole 24-hour recordings. HR did not differ between patients and controls. Time-domain parameters SDNN, SDNNi, rMSSD, and pNN50% were significantly decreased in frontal lobe patients when compared to controls. SDANN was comparable between groups. SDNN, rMSSD, and pNN50% were calculated for waking and sleep periods and used to analyze HRV during these states. These three parameters were significantly decreased during wakefulness in the patients' group but no statistical difference was seen during sleep. A further analysis was done to compare the intragroup behavior of HRV parameters during wakefulness and sleep. During sleep, a tendency to an increased HRV was seen in both groups, but only the control group showed a significant increase in rMSSD and pNN50%. Main results are shown in Tables 3 and 4.

The 24-hour Holter HRV time-domain parameters were all inversely and significantly correlated to the SUDEP-7 scores. SDANN showed the most strong and significant correlation. When periods of wakefulness and sleep were distinctly separated, no correlation was seen between these parametres and SUDEP-7 scores during wakefulness, while they were strongly correlated during sleep. The correlation between sleep rMSSD and SUDEP-7 was particularly robust. Among frequency-domain parameters, LF was significantly correlated to SUDEP-7 scores. Table 5 resumes these findings.

As for subgroup comparisons, active epilepsy was associated with sleep SDNN significant decrease. Cognitive deficit was associated with a decrease in pNN50 and sleep pNN50, as well as in LH. A tendency to a decreased SDANN and sleep rMSSD was also seen. Having presented at least three generalized seizures the previous year was associated with decreased SDANN. Medication load and time-length of epilepsy were not associated with any HRV parameter modification. These results are found in Table 6.

MRI imaging	Medication	SUDEP-7 score
Bilateral frontal pachygyria.	valproate, carbamazepine, levetiracetam, clobazan	8
Right III ventricle enlargement	phenobarbital	7
Right frontal white matter signal increase (FLAIR/T2). Right external capsule gliosis.	carbamazepine	1
Normal	carbamazepine, lamotrigine	2
Normal	valproate, lamotrigine	3
Hemorrhagic cyst on the right choroidal fissure.	carbamazepine	2
Left frontal white matter signal increase (T2 e/FLAIR).	Carbamazepine, phenobarbital, levetiracetam, clobazan	5
Right perisylvian polymicrogyria.	carbamazepine, lamotrigine, levetiracetam, clobazan	6
Left fronto-parietal schizencephaly	Oxcarbazepine, lamotrigin, valproate	7
Right frontal lobe signal increase (T2/FLAIR). (Sequelae of surgical drainage of two abscesses).	divalproate, carbamazepine	7

TABLE 2 Body mass index distribution among patients and controls

BMI	Minimum	1st Quartile	Median	Mean	3rd Quartile	Max.	NA's
Controls	19.4	21,5	24,4	24,46	26,3	31.2	
Patients	18	20,28	29,1	27,4	31,75	38	1

Note: Wilcoxon test, *P*-value: 0.3175.

TABLE 3 Comparison of HRV parameters among patients and controls. Results are expressed in medians and interquartile differences (IQD)

HRV parameters	PATIENTS (median/ IQD)	CONTROLS (median/IQD)	*P*-value
HR (medium) (bpm)	85.50/ 12.25	80.00/ 9.00	.231
RR Intervals (ms)	685.30/ 110.20	762.20/ 86.8	.196
SDNN (ms)	102.50/ 15.75	126.00/ 41.50	**.034**
SDNNi (ms)	40.50/ 11.50	56.00/ 15.50	**.009**
SDANN (ms)	96.00/ 12.50	120.00/ 47.50	.291
rMSSD (ms)	19.50/ 9.25	29.00/ 10.00	**.034**
pNN50 (%)	2.50/ 3.50	6.00/ 7.50	**.039**
SDNN Wakefulness (ms)	80.00/ 28.25	118.00/ 27.50	**.011**
rMSSD Wakefulness (ms)	15.50/ 6.50	26.00/ 10.00	**.007**
pNN50 Wakefulness (%)	0.26/ 1.75	4.00/ 6.50	**.002**
SDNN Sleep (ms)	96.50/ 18.50	97.00/ 41.50	.697
rMSSD Sleep (ms)	27.00/ 22.75	36.00/ 12.50	.126
pNN50 Sleep (%)	6.50/ 7.25	14.00/ 13.00	.125
LF	350.10/154.10	649.4/280.50	.055
HF	105.20/88.20	210.00/205.70	.095
LF/HF	2.80/2.80	2.70/2.20	.531

TABLE 4 Intragroups Comparison of HRV in Wafefulness and Sleep. Results are expressed in medians and interquartile differences (IQD)

HRV parameters	Wakefulness (median/ IQD)	Sleep (median/ IQD)	*P*-value
Patients			
SDNN (ms)	69.50/ 24.07	90.50/ 48.46	.272
rMSSD (ms)	13.00/ 7.94	19.25/ 28.80	.053
pNN50 (%)	0.00/ 4.30	0.50/ 12.16	.100
Controls			
SDNN (ms)	94.00/ 31.39	89.50/ 38.36	.724
rMSSD (ms)	22.50/ 7.30	26.50/ 16.10	**.046**
pNN50 (%)	2.00/ 4.62	4.00/ 12.95	**.041**

4 | DISCUSSION

The primary findings of this study are that time-domain HRV and vagus-mediated HRV measures are significantly reduced in FLE patients versus normal controls. In addition, HRV measures in FLE patients were significantly correlated with risk for SUDEP, as measured by the SUDEP-7 inventory.

Significant reductions in the following HRV measures were found in FLE patients when compared to controls: SDNN, SDNNi, rMSSD, and pNN50 during the 24-hour recordings and SDNN, rMSSD, and pNN50 during wakefulness. SDNNi showed the highest discrepancies between patient and control groups. It estimates variability due to the factors affecting HRV within a 5-minute period and primarily represents the autonomic influence upon HRV.[23] The very low rMSSD values found among patients, translating a decrease in parasympathetic activity, are similar to those reported in heart failure and predictive of higher mortality.[24] SDANN did not significantly differ between groups. Low SDANN has been associated with worse prognosis in ischemic heart disease, but it is mostly related to the amount of physical activity.[15,16] There was a tendency for increased HRV in both patients and controls during sleep. Only during wakefulness did we see a significant increase in SDNN, rMSSD, and pNN50 in controls compared to patients. This may signify a protective role for sleep even for patients with FLE,[25,26] prone to seizure facilitation during sleep.[7,27-29] Nevertheless, the parasympathetic parameters rMSSD and pNN50 increase during sleep were significantly more efficacious in healthy controls. These findings on sleep HRV behavior add to the previous work by Harnod et al, 2009, who registered waking 5-minute holter-EKGs and found interictal faster heart rates and decreased vagal tone in FLE patients.[4]

TABLE 5 Spearman correlation between HRV parameters and SUDEP-7 scores

Parameter	Median	IQD	Mean	SD	ρ	*P*-value
SDNN (ms)	103.00	14.50	108.36	23.05	**−0.716**	**.01321**
SDNNi (ms)	44.00	16.50	44.00	12.74	**−0.705**	**.01537**
SDANN (ms)	96.00	12.00	100.36	24.74	**−0.896**	**.00019**
rMSSD (ms)	23.45	10.50	23.45	10.06	−0.665	**.02552**
pNN50 (%)	3.00	4.00	3.91	5.41	**−0.727**	**.01120**
SDNN Wakefulness (ms)	88.0	25.50	126.31	120.28	−0.122	.73640
rMSSD Wakefulness (ms)	17.00	7.00	18.78	8.19	−0.527	.14450
pNN50 Wakefulness (%)	0.00	2.00	2.11	4.54	−0.416	.26500
SDNN Sleep (ms)	99.00	18.00	100.67	50.62	**−0.815**	**.00742**
rMSSD Sleep (ms)	27.00	10.00	27.66	20.85	**−0.945**	**.00012**
pNN50 Sleep (%)	6.00	7.00	7.78	12.58	**−0.884**	**.00155**
LF	370.10	149.90	456.40	292.12	**−0.832**	**.00284**
HF	124.35	89.95	189.96	249.83	−0.606	.06357
LF/HF	2.80	2.45	3.46	1.55	0.0399	.91290

Frequency-domain parameters did not differ between groups, although a tendency was seen for increased HF and LF among controls when compared to patients.

FLE patients' 24-hour recording derived time-domain parameters were inversely and significantly correlated to SUDEP-7 scores. Previously, DeGiorgio et al (2010) and Novak et al (2015) found rMSSD from pharmacoresistant focal epilepsy patients to be inversely correlated to SUDEP-7 (Pearson $r = -0.64$, $P = .004$) or to a modified SUDEP-7 (Pearson $r = -0.43$, $P = .0351$), respectively,[6,18] with a lower baseline rMSSD for patients with mental disability and higher age and disease duration. Our patients' median rMSSD was very low and comparable to that found by Novak et al, 2015.[6] Low levels of rMSSD mean a decrease in vagal tone regulation to the heart and may either decrease the RR intervals and facilitate cardiac conduction reentrance networks causing tachyarrhythmia or leave the heart to a rebound "paradoxical" excessive vagal tone increase during a seizure causing bradyarrhythmia, conduction block or asystole, all of which have been registered with seizures.[30-32] Repeated seizures may lead to transient myocardial ischemia and Takotsubo syndrome.[20] As regards interictal activity, animal models using discrete cortical electrical events had time-locked alteration in the autonomic nervous activity.[33,34] One study reviewed surface EEG from non-lesional focal epilepsy patients and compared RR intervals timely locked to interictal epileptiform discharges to RR intervals immediately following interictal activity. The first were changed, with most shortenings for left sided and lengthenings for right sided interictal discharges.[35]

SDANN was also strongly and inversely correlated to SUDEP-7 (Spearman $\rho = -0.896$, $P = .00019$). The autonomic contribution to this parameter is disputed, but knowledge derived from studies on ischemic heart disease says that significant increases occur by changing physical activity levels from enforced rest to scripted activity. Increases in SDANN parallel improvements in functional capacity and predict a favorable long-term outcome, whereas a decline in physical activity corresponds to a decrease in SDANN prior to clinical deterioration.[36] After subgroup analysis, having had at least three generalized tonic-clonic seizures during the previous year was associated with a decreased SDANN. Patients with generalized seizures tend to be more reclusive and engage less often into social and sports activities. This suggests that the level of physical activity of patients with FLE should itself be evaluated as a risk factor for SUDEP. LF was also inversely and significantly correlated to SUDEP-7 scores, signifying that a sympathetic dysfunction may also be important in building SUDEP risk in FLE.

SDNN, rMSSD, and pN50 were distinctly evaluated for periods of wakefulness and sleep. There was no correlation to SUDEP-7 scores for the former, whereas sleep time-domain parameters were highly and inversely correlated to SUDEP-7, particularly rMSSD (Spearman $\rho = -0.945$, $P = .00012$). Active epilepsy was associated with decreased sleep SDNN. A tendency to lower rMSSD was seen for patients with cognitive deficit, although not reaching statistical significance as in Novak et al 2015[6] but a significant decrease in pNN50, another marker of vagal activity, particularly during sleep, was associated with this group, as was LF decrease. HRV studies during sleep hours may fundamentally increase the chance of identifying FLE patients at risk for SUDEP.

We compared FLE patients to healthy individuals to generate data on that particular type of epilepsy affecting heart rhythms and secure that findings were not common to the general population. We elected a control group taking into account confounders known to affect cardiac autonomic regulation, such as body mass index, age and gender. Increased body mass index decreases HRV, in particular when central adiposity is present.[37] Moreover, a comparable distribution of age and gender was assured as it was previously shown that older individuals have lower HRV compared to younger ones and that female gender is associated with higher HF and lower LF/HF.[38,39]

TABLE 6 Comparative HRV parameters values among subgroups

HRV	AE	IA	*P*-value	CD	No CD	*P*-value
SDNN (ms)	101/14.00	108/21.50	0.200	89.00/11.00	107.50/14.75	0.125
SDNNi (ms)	35/13.00	45/15.50	0.247	32.00/8.00	45.50/19.75	0.085
SDANN (ms)	90/13.00	99.5/16.0	0.143	83.00/8.50	98.00/10.50	0.052
rMSSD (ms)	18/5.00	24/8.75	0.410	17.00/3.50	25.00/9.75	0.082
pNN50 (%)	2.00/2.00	3.50/4.74	0.579	0.00/0.50	3.50/2.50	**0.049**
SDNN w (ms)	82.00/21.00	94.00/27.00	1.000	82.00/8.00	99.00/48.50	0.833
rMSSD w (ms)	15.00/5.00	18.00/12.00	0.460	17.00/3.00	17.00/11.25	0.604
pNN50 w (%)	0.50/1.25	0.00/2.00	1.000	0.00/0.50	1.00/2.00	0.477
SDNN Sleep (ms)	91.00/26.25	110.00/18.00	**0.032**	90.00/51.00	104.50/22.25	0.167
rMSSD Sleep (ms)	22.00/14.25	29.00/13.00	0.176	17.00/10.00	28.00/5.00	0.052
pNN50 Sleep (%)	3.00/6.25	7.00/6.00	0.317	0.00/0.00	7.00/1.50	**0.025**
LF	350.10/252.70	390.10/270.30	0.421	210.40/58.30	463.10/167.40	**0.033**
HF	143.50/65.00	105.20/88.20	1.000	62.60/24.50	150.80/44.15	0.067
LF/HF	2.80/0.40	5.20/3.00	0.402	4.00/1.55	2.80/1.70	1.000

Note: AE, active epilepsy; AEM, antiepileptic medication; CD, cognitive deficit; GTCS, generalized tonic-clonic seizure; IE, inactive epilepsy; py, previous year; w, wakefulness; y, year.

Results are expressed in medians/interquartile differences. Wilcoxon test was used.

A major drawback to HRV methodology, however, is the lack of established normative values for the normal population according to age.[40] In this study, disadvantageous prognosis values related to SDNN, rMSSD, and pNN50 were seen in three patients, but four control volunteers also showed very decreased pNN50 values. Interpretation of such findings and inferences on patients with epilepsy based on HRV values with prognostic significance for ischemic heart disease will very much depend on studies done on large healthy populations.

The main limitation to this study is the low number of patients enrolled, although that assured a patient group without comorbidities, as well as the heterogeneity linked to putting lesional and non-lesional patients together or to possible different medication effects.[41-44]

FLE is prone to seizures during sleep, and many deaths from SUDEP have followed nocturnal seizures.[45] Some case reports demonstrate SUDEP in young patients with FLE.[46,47] SUDEP rate for nocturnal FLE was not higher than that from prevalent epilepsy populations (0.4-2.3 per 1000 person-years),[29] but this particular population lacks generalized seizures.[18,22] One study identified 9 SUDEP-related deaths from 2309 patients with active epilepsy, three having had definite FLE and one possible FLE.[48]

This study showed that HRV is impaired in patients with FLE, whose low HRV scores are associated with increased risk for SUDEP as measured by the SUDEP-7 score. HRV studies during sleep may increase the chance of identifying FLE patients at risk for SUDEP.

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CONFLICTS OF INTEREST

Dr Glenda Corrêa Borges de Lacerda received speaker fees from Torrent Pharmaceutical Industry in January 2017. This activity was not related to the submitted work. Other authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. Publicity of data was not considered by the Ethics Comittee.

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≥3 GTCS/ py	<3GTCS/py	*P*-value	≥3AEM	<3AEM	*P*-value	≥30 y	<30 y	*P*-value
89.00/10.50	108.00/14.75	0.082	95.00/11.50	103.50/14.75	0.413	103.00/4.50	106.50/18.25	0.759
32.0.0/14.00	44.50/12.25	0.279	34.00/8.50	45.00/19.75	0.194	44.00/11.0	41.00/14.50	1.00
83.00/7.50	98.00/10.00	**0.032**	89.00/8.50	96.00/13.50	0.357	90.00/1.50	98.00/12.25	0.260
17.00/10.50	21.00/9.25	0.474	17.00/4.00	24.00/10.50	0.260	19.00/9.50	21.00/10.25	0.919
1.00/2.50	3.00/2.99	0.606	1.00/1.50	3.50/3.75	0.302	0.00/2.50	3.00/2.75	0.353
82.00/192.55	94.00/29.50	0.667	78.00/11.00	94.00/46.00	0.667	94.00/193.05	82.00/29.00	0.667
14.50/2.50	18.00/9.50	0.378	17.00/4.00	16.00/10.75	0.795	15.00/3.00	17.00/9.50	0.557
0.50/0.5	0.00/2.00	0.872	1.00/1.00	0.00/1.50	0.776	0.00/0.00	1.00/2.00	0.259
45.00/45.00	102.00/18.50	0.055	94.00/4.50	106.00/23.00	0.381	98.00/4.00	99.00/24.00	1.000
8.50/8.50	27.00/7.50	0.056	19.00/5.00	28.00/10.25	0.299	19.50/0.5	27.00/9.00	0.462
0.00/0.00	7.00/3.50	0.099	2.00/3.50	6.50/6.25	0.598	1.00/1.00	7.00/4.50	0.295
210.40/126.95	390.10/199.55	0.183	324.80/134.25	390.10/191.65	0.517	325.80/69.15	390.10/257.25	0.667
100.90/57.00	143.50/77.05	0.517	100.90/56.45	143.50/74.45	0.833	62.60/53.85	143.50/57.90	0.517
2.80/0.95	2.80/2.90	0.732	2.80/1.75	2.80/2.10	1.000	5.20/1.40	2.60/1.15	0.209

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