FULL-LENGTH ORIGINAL RESEARCH

Heart rate variability in untreated newly diagnosed temporal lobe epilepsy: Evidence for ictal sympathetic dysregulation

*†Andrea Romigi, *†Maria Albanese, *Fabio Placidi, *Francesca Izzi, *‡Nicola B. Mercuri, *Angela Marchi, *Claudio Liguori, *Nicoletta Campagna, §Andrea Duggento, §Antonio Canichella, *Giada Ricciardo Rizzo, §Maria Guerrisi, ¶Maria G. Marciani, and §**††Nicola Toschi

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Andrea Romigi is a clinical epileptologist and sleep specialist.

Summary

Objective: To compare heart rate variability (HRV) parameters in newly diagnosed and untreated temporal lobe epilepsy (TLE) between the interictal, preictal, ictal, and postictal states.

Methods: HRV parameters were extracted from single-lead electrocardiography data collected during video–electroencephalography (EEG) recordings from 14 patients with newly diagnosed TLE in a resting, awake, and supine state. HRV parameters in the time and frequency domains included low frequency (LF), high frequency (HF), standard deviation of all consecutive R wave intervals (SDNN), and square root of the mean of the sum of the squares of differences between adjacent R wave intervals (RMSSD). Cardiovagal index (CVI), cardiosympathetic index (CSI), and approximate entropy (ApEn) were also studied.

Results: Frequency domain analysis showed significantly higher preictal, ictal, and postictal LF/HF ratio compared to the interictal state. Similarly, the LF component increased progressively and was significantly higher during the ictal state compared to interictal and preictal states. RR interval values were lower in the ictal state compared to basal and preictal states and in the postictal state compared to the preictal state. Interictal RMSSD was significantly higher compared to all other states, and ictal SDNN was significantly higher compared to all other states. Ictal CSI was significantly higher compared to preictal and interictal states, whereas preictal CVI was lower than in basal and ictal states. In addition, ictal ApEn was significantly lower than interictal and preictal ApEn. Interictal CVI was lower in left TLE compared to right TLE. In addition, in left TLE, ictal CVI was higher than interictal CVI, whereas in right TLE, CVI was lower in the preictal state compared to all other states.

Significance: Our data suggest an ictal sympathetic overdrive with partial recovery in the postictal state. Higher sympathetic tone and vagal tone imbalance may induce early autonomic dysfunction and increase cardiovascular risk in patients affected by TLE.

KEY WORDS: Heart rate variability, Temporal lobe epilepsy, Autonomic nervous system.

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*Department of Systems Medicine, Neurophysiopathology Unit, Sleep Medicine Centre, Tor Vergata University and Hospital, Rome, Italy; †IRCCS Neuromed Sleep Medicine Centre, Pozzilli, Italy; ‡Santa Lucia Foundation, Rome, Italy; §Department of Biomedicine and Prevention, Medical Physics Section, University of Rome "Tor Vergata," Rome, Italy; ¶Department of Neuroscience, "Tor Vergata," University, Rome, Italy; **Department of Radiology, Athinoula A. Martinos Center for Biomedical Imaging, Boston, Massachusetts, U.S.A.; and ††Harvard Medical School, Boston, Massachusetts, U.S.A

Address correspondence to Andrea Romigi, Department of Neurophysiopathology, University of Rome "Tor Vergata", Policlinico Tor Vergata, Sleep and Epilepsy Centre, Viale Oxford 81, Zip code 00133, Rome, Italy. E-mail: a_romigi@inwind.it

Key Points

- Newly diagnosed untreated temporal seizures induce a sympathetic overdrive as shown by significant increase of LF/HF ratio, LF, SDNN, and CSI
- Left-sided TLE involves a lower basal vagal tone when compared to right-sided TLE. Ictal vagal tone in left-sided TLE is higher than in the basal state, whereas in right-sided TLE, preictal vagal tone is lower than in the basal state, confirming asymmetric representation of autonomic function
- Our data suggest the existence of an ictal sympathetic overdrive with partial recovery in the postictal state, which is more evident in left temporal seizures
- We speculate that higher sympathetic tone, concurrent with vagal tone imbalance, may increase cardiovascular risk in temporal seizures
- Our findings may suggest an early autonomic involvement in untreated temporal seizures

Heart rate variability (HRV) changes in epilepsy comprise both ictal and interictal autonomic cardiac effects.[1–3] Interictal autonomic abnormalities include combined inhibition[2,4,5] or suppression[6] of both sympathetic and parasympathetic tone, suppression of sympathetic or parasympathetic tone, low parasympathetic, and high sympathetic tone.[7,8]

These autonomic alterations are independent of sex, age, and type of epilepsy,[2–5] but appear to be more severe in patients with long-lasting and refractory epilepsy.[3,9] Ictal tachycardia, bradycardia, asystole, shortening of QT interval, atrial fibrillation, T-wave inversion, and/or ST interval elevation/depression have been described previously during seizures, particularly when these are prolonged, generalized, and originating from the temporal lobe.[10] Although the mechanisms leading to autonomic alterations and cardiac changes in epilepsy are not yet well understood, some authors have hypothesized an activation of the central autonomic network, mainly involving the insular cortex and temporal-mesial structures, induced by the spread of repetitive seizures discharges.[11,12]

In addition, cardiac events and/or central hypoventilation have been suggested as possible contributing factors in sudden unexpected death in epilepsy (SUDEP).[13–15] Although polytherapy or frequent medication changes as well as a higher number of generalized tonic–clonic seizures has been proposed as one of the most important risk factors for SUDEP,[15] recently a reduction in HRV, which is consistently related to arrhythmias and increased cardiovascular risk, has been associated with SUDEP in refractory temporal lobe epilepsy (TLE).[16,17]

To date, little is known about ictal HRV changes in untreated patients with newly diagnosed TLE. The objective of our study was to assess the effects of temporal lobe seizures on the autonomic nervous system (ANS) in untreated and newly diagnosed TLE while explicitly separating different conditions (interictal, preictal, ictal, and postictal). This study was designed to evaluate the effect of TLE itself on ANS activity (as assessed through HRV measures) while excluding confounding factors that are commonly arduous to factor out and/or control for (i.e., polytherapy, drug refractoriness, and long disease duration), as well as to identify potential autonomic markers of seizure onset.

Methods

Patients affected by TLE in accordance with International League Against Epilepsy (ILAE) guidelines[18] were retrospectively selected from the database of patients who underwent video–electroencephalography (EEG) monitoring of Sleep & Epilepsy Center of the University General Hospital of Rome Tor Vergata. All patients received a diagnosis of TLE based on comprehensive clinical, neuropsychological, interictal, and ictal video-EEG, as well as brain magnetic resonance imaging (MRI) evaluations as part of the diagnosis process in order to ascertain symptomatic or cryptogenic TLE. We evaluated patients who underwent video-EEG monitoring during the initial diagnostic process and were therefore still untreated. The diagnosis of TLE was based on the confirmation of an ictal onset in either temporal region, on the presence of temporal lobe interictal EEG abnormalities, and on clinical semiology consistent with TLE. To this end, video-EEG monitoring records were reviewed by expert epileptologists (AR and FI) and EEG and/or clinical criteria were used to define start of the seizure. This study was approved by the institutional review board (IRB) of the University of Rome Tor Vergata. Given that this was a retrospective study, the IRB specifically waived the need for consent of participants. Data were anonymized by removal of direct identifiers from the data file and also deidentified prior to analysis.

Inclusion criteria were as follows: new diagnosis of epilepsy documented by neurologic examination and brain MRI, and at least one seizure originating from temporal regions recorded by video-EEG monitoring. Exclusion criteria were the following: (1) previous or ongoing treatment with antiepileptic drugs (AEDs); (2) intake of drugs interfering with ANS function; (3) history of heart failure, endocrine disorders, metabolic deficits, uremia, or any other known disease that might affect autonomic function; (4) sleep-related breathing disorders. All video-EEG sessions were independently evaluated by an expert epileptologist (AR) as well as by a neurophysiologic trainee (MA), who selected only seizures occurring at rest and during wakefulness in the supine state, with artifact-free preictal, ictal, and

postictal electrocardiography (ECG). We defined four conditions based on the consensus between the two evaluations:

1 Interictal (INT): 2 min of artifact-free resting ECG obtained before seizures and during wakefulness
2 Preictal (PRE): 2 min of artifact-free ECG immediately before seizure onset
3 Ictal (ICT): artifact-free ECG immediately after seizure onset and comprising the entire seizure duration
4 Postictal: (POST) 2 min of artifact-free ECG immediately after seizure end.

ECG samples and RR series construction

Bipolar ECG recording from lead I of a 12-lead ECG were carried out by means of the ECG channel of the EBN-Neuro EEGNet System (EBNNeuro – Florence Italy). ECG data were sampled at a frequency of 256 Hz and exported from the EBN system (EEGNET, Florence, Italy) in the European Data Format (EDF). All subsequent processing was performed off-line using custom-built code in Labview 2013 and Mathematica 10.1. This entailed QRS complex detection and R peak identification using a multiscale wavelet-based peak detection algorithm, construction of an RR interval (RRI) time series by measuring the interval between consecutive R waves, and resampling of the RRI series at a frequency of 8 Hz using cubic splines as basis functions. Before interpolation and resampling, all RRI series were visually inspected in conjunction with the original ECG trace for removal of erroneously detected R waves and insertion of missed R beats. In addition, ectopic beats were deleted and replaced by a virtual beat by interpolating adjacent R waves as recommended.[19]

HRV analysis

To forego the assumption of stationarity, which is mandatory for traditional, Fourier transform–based methods to be applicable, we chose to analyze the interpolated and resampled RRI series using a time–frequency decomposition method. After making the signal analytic through Hilbert transformation, for each RRI series, a time–frequency representation of the signal was obtained by computing its Smoothed Pseudo-Wigner-Ville distribution (time smoothing window: Hamming window of 42 samples; frequency smoothing window: Hamming window of 79 samples).[20] For each condition, a total signal length of 4 min (1 min before and 1 min after the period under investigation) was entered into the analysis. The time–frequency representation was successively constrained to the 30 s central to the 2 min period (or in the case of ICT, central to the seizure period) defined earlier. In the two seizures that were slightly shorter than 30 s (28 s and 20 s, see Table 1), the entire sei-

Table 1. Demographic and clinical data of whole patient population

Pts	Gender	Age	Lateralization	Disease duration	Secondary generalization	Etiology	Seizures (n)	Ictal semiology	Seizure duration (s)
1	M	61	Right TLE	6 m	Y	Symptomatic (low grade glioma)	2	Epigastric sensation, left upper limb paresthesias	40″, 35″
2	M	62	Left TLE	6 m	Y	Cryptogenic	2	Psychomotor arrest, tachycardia	40″, 30″
3	F	49	Right TLE	12 m	N	Symptomatic (Cavernous angioma)	1	Psychomotor arrest	28″
4	M	52	Right TLE	3 m	Y	Cryptogenic	2	Confusion, dizziness	40″, 20″
5	F	36	Left TLE	10 m	Y	Cryptogenic	1	Psychomotor arrest, aphasia	40″
6	M	40	Right TLE	20 m	N	Cryptogenic	1	Psychomotor arrest	50″
7	F	56	Left TLE	1 m	N	Cryptogenic	1	Epigastric aura, confusion	30″
8	M	60	Left TLE	20 m	Y	Symptomatic (low grade glioma)	1	Psychomotor arrest, aphasia	80″
9	F	30	Left TLE	3 m	N	Cryptogenic	1	Oroalimentary automatisms, psychomotor arrest	60″
10	F	42	Left TLE	12 m	N	Cryptogenic	1	Fear, anxiety sensation	80″
11	F	63	Left TLE	10 m	N	Cryptogenic	1	Confusion	30″
12	M	45	Left TLE	12 m	N	Symptomatic (cavernous angioma)	2	Psychomotor arrest, expressive aphasia	70″, 50″
13	F	35	Right TLE	7 m	Y	Cryptogenic	2	Confusion, psychomotor arrest	60″, 48″
14	F	51	Right TLE	2 m	Y	Cryptogenic	2	Confusion, psychomotor arrest	30″, 45″

zure duration was selected and the signal length was matched in the corresponding INT, PRE, and POST segments. Successively, average low frequency power (LF, 0.04–0.15 Hz) and high frequency power (HF, 0.15–0.4 Hz) were obtained by time-averaging for each subject and each condition. LF reflects the modulations of the sympathetic and the parasympathetic nervous system, whereas HF mainly reflects parasympathetic nervous system activity.[21] The LF/HF ratio expresses the balance between sympathetic and parasympathetic nervous system activity. The very low frequency (VLF, ≤0.04 Hz) component was not evaluated in our study because it requires longer term ECG monitoring. Two time domain measures of HRV were also calculated: SDNN (standard deviation of all NN intervals) and RMSSD (root mean square of the difference of adjacent NN intervals). SDNN represents a global measure of HRV and provides information about all HRV components. RMSSD is considered a powerful measure of HF variations in short-term recording, as it provides a useful evaluation of HF and vagal tone.[19] Given the dependence of SDNN on record length,[19] SDNN values should be compared to SDNN obtained from recordings with similar duration. We also calculated two indices derived from the Poincarè Plot of the RRI series (in which each RRI is plotted against the following RRI): the cardiovagal index (CVI = Log10 [L · T]) and cardiosympathetic index (CSI = L/T).[22,23] The length of the transverse axis (T) in the Poincarè Plot reflects beat-to-beat variability, with deviations along this axis predominantly reflecting parasympathetic system influence. The length of the longitudinal axis (L) reflects the overall range of RRIs due to both sympathetic and parasympathetic influences.[23] It has been suggested that these indices provide complementary information about parasympathetic and sympathetic contributions to HRV when compared to parameters based on spectral analysis alone.[22] Finally, we calculated the approximate entropy (ApEn), which detects differences in heart rate data that are not visually apparent. ApEn is a measure of regularity versus randomness and quantifies the predictability of fluctuations in a time series (such as the RRI time series).[23]

Statistical analysis

Data normality was checked using the Mardia Coefficient of Multivariate Kurtosis, after which all HRV-related indexes were compared across groups and conditions using a general linear model (GLM), which modeled subject means as a "between" factor and also contained one 2-level "within" factor ("side": Right, Left) and one 4-level "within" factor ("state": INT, PRE, ICT, POS). Whenever the overall effect of a factor was seen to be statistically significant ($p < 0.05$), we employed Newman-Keuls as a post hoc test, which incorporates a stepwise correction for multiple comparisons. The GLM also contained age and gender as nuisance covariates. All values of $p < 0.05$ (corrected) were considered statistically significant in post hoc testing. Statistical analysis was performed using the Statistica 10.0 software (Statsoft, U.S.A.).

Results

Subjects

Fourteen (26%) of a total 52 subjects were eligible for the study (six male, eight female, mean age 41.5 ± 21.05). To exclude events and/or conditions that may have affected HRV analysis, 38 patients were excluded from the study according to the following criteria: motor activity and/or not completely supine position during seizure (n = 14); ECG artifacts in one or more conditions (INT/PRE/ICT/POST) (n = 15); and both the aforementioned conditions (n = 9). Clinical and demographic features are summarized in Tables 1 and 2. All patients were right handed. We defined ictal onset as the first visible clinical manifestation of the seizure and/or the identification of ictal EEG patterns. We collected 20 seizures suitable for HRV analysis (10 left-sided TLE, 10 right-sided TLE). No more than two seizures per patient were included in the analysis. We did not find any statistically significant difference between right and left TLE patients when testing age ($p = 0.84$), sex ($p = 1$), disease duration ($p = 0.16$), and history of secondarily generalized seizures ($p = 0.32$) (Table S1). All patients had interictal epileptiform activity ipsilateral to the seizure onset. In addition, left and right temporal seizures were similar for duration ($p = 0.14$), propagation pattern (3 of 10 seizures in both right and left temporal seizures), and delay of propagation (right [n = 3] 16 ± 6.9 s vs. left [n = 3] 21 ± 11.5 s – note that due to low numerosity [n = 3] this mean difference was not tested statistically) (Table S1). RR interval series from two exemplary seizures are shown in Figure 1.

Effect of "state"

The analysis of HRV spectral components showed that the LF/HF ratio was significantly higher in the PRE ($p = 0.0002$), ICT ($p < 0.0001$), and POST ($p < 0.0001$)

Table 2. Demographic and clinical data summarized by lateralization

	Right TLE (n = 6)	Left TLE (n = 8)	p-Value
Age (years)	48 ± 9.2	49.2 ± 12.7	0.84
Sex (M/F)	3/3	3/5	1
Disease duration (months, range)	9 ± 8.14 (3–24)	9.25 ± 5.97 (1–20)	0.94
Secondary generalization (Y/N)	4/2	4/8	0.32

Interaction between lateralization and clinical/demographical variables in right TLE and left TLE patients. Chi-square test for categorical variables (sex and the presence of a history of secondarily generalized seizures); Student *t*-test for age and disease duration. $p < 0.05$ was considered statistically significant.

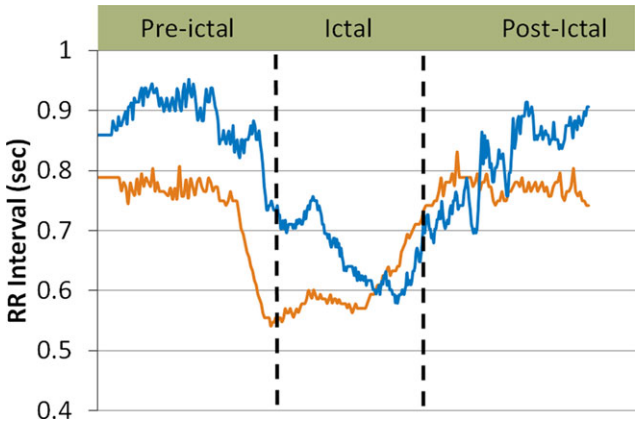

Figure 1.
Time-course of RR interval in two exemplary seizures (orange and blue), including preictal and postictal periods.
Epilepsia © ILAE

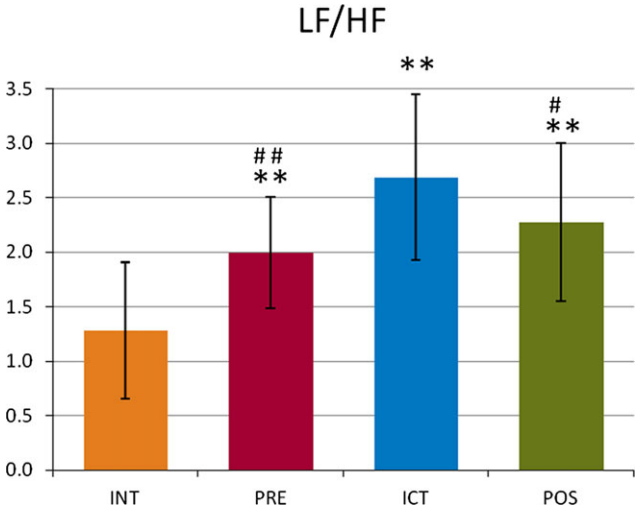

Figure 2.
LF/HF ratio across states (INT, PRE, ICT, and POST). **p < 0.01 in post hoc comparison with INT. ##p < 0.01 in post hoc comparison with ICT; #p < 0.05 in post hoc comparison with ICT.
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states compared to the baseline state (INT) and in ICT versus PRE (p = 0.00029) and POST (p = 0.02) (Fig. 2). The LF component increased progressively and reached its highest values in the ICT state versus INT (p = 0.04) and PRE (p = 0.01); significant increase as a function of state was also found in the HF component in ICT versus INT (0.01) and ICT versus PRE (0.003) (Table 3).

Similarly, RRI was significantly lower in the ICT state compared to INT (p = 0.000007) and PRE (p = 0.000001), in POST compared to PRE (p = 0.0005), and in POST compared to INT (p = 0.004). SDNN was significantly higher in the ICT state compared to PRE (p = 0.00009), POST (p = 0.01), and INT (p = 0.0006) states. RMSSD was significantly higher in INT compared to PRE (p = 0.001), ICT (p = 0.02), and POST (p = 0.01) (Table 3).

Moreover, CSI was significantly higher in ICT versus PRE (p = 0.0007) and INT (p = 0.000002) states, with a visible lack of full recovery to baseline in the POST condition as compared with INT (p = 0.03). CVI values were significantly reduced in PRE versus INT (p = 0.003) and PRE versus ICT (p = 0.0006). ApEn was significantly reduced in ICT compared to INT (p < 0.00001) and PRE (p = 0.000003), with a partial recovery in POST compared to INT (p = 0.005) (Table 3). All subjects with two recorded seizures showed the same HRV trends.

Effect of "side"

When analyzing hemispheric lateralization, we found that CVI was significantly reduced in patients with left-sided TLE compared to right-sided TLE in the basal state (INT) (p = 0.03). Other HRV-parameters were not influenced by the side of epileptiform discharge-pattern (Table 4).

In left-sided TLE we found higher SDNN during ICT when compared to INT (p = 0.0001), PRE (p = 0.002), and POST (p = 0.0007) states. In addition, in left-sided TLE, ictal CVI was significantly higher when compared to INT (p = 0.03) (Table S2). On the other hand, in right-sided TLE, preictal CVI was reduced when compared to INT (p = 0.00005), ICT (p = 0.002), and POST (p = 0.01). In addition, in right-sided TLE, SDNN was significantly higher during ICT (p = 0.008) and POST (p = 0.01) when compared to PRE (Table S3).

Discussion

Effects of temporal lobe seizures on HRV parameters

Our data confirm the hypothesis of a sympathovagal imbalance related to temporal seizures in patients with newly diagnosed and untreated epilepsy, visible as changes in RRI, LF, HF, LF/HF ratio, RMSSD, CSI, CVI, and ApEn. We observed a significant increase of LF/HF ratio in PRE, ICT, and POST when compared to INT, thus compatible with a lack of a complete postictal recovery to baseline. Ictal LF/HF ratio was also significantly increased versus PRE and POST. Similarly, ictal LF and HF were increased compared to both INT and PRE. In addition, ictal CSI was significantly higher than in INT, PRE, and POST, also compatible with a lack of a complete recovery in POST. Similarly, RRI was lower in ICT versus INT and PRE, and RRI was also lower in POST versus PRE and INT. In addition, a decrease of CVI during PRE versus ICT and INT was found. These findings are intriguing because they reflect a combined seizure-induced activation of the sympathetic nervous system, possibly preceded by a preictal reduced vagal tone. This could suggest that inputs from cortical and/or subcortical structures involved in and/or affected by the epileptic discharge may account for sympathetic imbalance

Table 3. Differences in HRV metrics during each condition: general HRV parameters

	INT Mean ± SD	PRE Mean ± SD	ICT Mean ± SD	POST Mean ± SD	p-Value
LF (s^2)	0.67 ± 0.18	0.97 ± 0.29	2.91 ± 0.87[b,a]	1.96 ± 0.58	0.004[b]; 0.01[a]
HF (s^2)	0.58 ± 0.14	0.50 ± 0.11	1.15 ± 0.23[b,a]	0.84 ± 0.21	0.01[b]; 0.003[a]
LF/HF ratio	1.26 ± 0.13	2 ± 0.11[f]	2.68 ± 0.16[b,a,c]	2.29 ± 0.14[d]	0.0002[f]; <0.0001[b]; <0.0001[d]; 0.0002[a]; 0.02[c]
RR interval (s)	0.82 ± 0.01	0.83 ± 0.01[e]	0.73 ± 0.01[b,a]	0.77 ± 0.02[d]	<0.0001[b]; <0.0001[a]; 0.0005 0.004[e]
RMSSD (s)	0.10 ± 0.01	0.06 ± 0.01[f]	0.07 ± 0.01[b]	0.07 ± 0.007[d]	0.001[f]; 0.02[b]; 0.01[d]
SDNN (s)	0.03 ± 0.002	0.02 ± 0.002	0.04 ± 0.004[b,a,c]	0.03 ± 0.003	0.0006[b]; <0.0001[a]; 0.01[c]
CSI	7.12 ± 0.55	8.95 ± 0.65	12.7 ± 1.21[b,a,c]	10.3 ± 0.9[d]	<0.0001[b]; 0.002[d]; 0.0007[a]; 0.03[c]
CVI	3.41 ± 0.10	3.22 ± 0.05	3.47 ± 0.07	3.34 ± 0.07	0.003[f]; 0.0006[a]
ApEn	0.52 ± 0.01	0.48 ± 0.01	0.34 ± 0.02[a,b]	0.44 ± 0.01[d]	<0.0001[b]; 0.005[d]; <0.0001[a];

Level of significance p = 0.05. [a]PRE versus ICT; [b]INT versus ICT; [c]ICT versus POST; [d]INT versus POST; [e]PRE versus POST; [f]INT versus PRE.

in TLE.[24] This hypothesis could be verified through noninvasive brain stimulation techniques[25,26] and reflects recent insight from transcranial magnetic stimulation (TMS) and magnetoencephalography (MEG) studies, which demonstrate that in TLE, cortical excitability alterations are distributed widely beyond the epileptic focus.[27,28]

Present data exploring the interictal sympathetic control of HRV in untreated epilepsy are not consistent across studies.[7,9] Recently, a meta-analysis of HRV in epilepsy reported a lack of significant alterations of LF in epilepsy patients compared to controls; however, this parameter was found to be lower in patients with AEDs when compared to drug-free subjects.[29] The increase of ictal LF/HF ratio, LF, HF, CSI, and CVI observed in our patient sample, which was free from common confounding factors (e.g., long disease duration, AEDs, drug-resistance), may suggest an early involvement of the ANS in TLE seizures. We also observed an increased sympathetic activation during PRE and ICT and POST when compared to INT**.** This may represent an autonomic marker of both subtle cardiac rhythm changes and onset of seizures.

In addition, CVI values were significantly reduced when comparing PRE to INT and ICT, and we also observed a significant preictal, ictal, and postictal reduction of RMSSD (a marker of vagal tone) when compared to INT. In addition, the LF component of the RRI power spectrum increased progressively and reached its highest values during the ictal state. This result is consistent with previous data showing a marked decrease in vagal tone before and during a seizure in patients with TLE examined using HRV analysis.[29,30] In addition, we observed a significant reduction of RRI when comparing ICT to both PRE and INT, as well as when comparing POST to PRE. A low ictal RRI and a high ictal LF may reflect an impairment of the adaptive cardiac response to stressful events or sudden cardiovascular demands, also known as "*cardiac resilience.*"[31,32] Our findings, which are consistent with an impaired vagal recovery and sympathetic overdrive, may therefore indicate a predisposition to a "pro-arrhythmic" condition, which, in turn, may lead to an increased risk of SUDEP not only in patients with refractory or well-controlled and long-lasting temporal seizures,[24,32,33] but possibly also in untreated patients. Still, it should be noted that a clear-cut ECG predictor for SUDEP was not evident when comparing focal seizures from patients who died from SUDEP with data from living patients in a drug-resistant sample.[34]

Moreover, a lower ApEn value during ICT was observed when compared to INT and PRE, as well as in POST versus INT. When combined with data derived from time and frequency-domain HRV studies, the observation of a reduction of ApEn in RRI series during seizures confirms the ictal predominance of the sympathetic nervous system without a postictal recovery to the basal condition and may also aid in designing an initial, easy-to-use approach for seizure prediction. Our data are in line with a previously observed decrease of HRV after seizures which lasted up to 5–6 h,[35] indicating a long term postictal dysregulation of ANS in drug-resistant presurgical patients. In addition, a previous paper evaluated the time course of autonomic disturbances after both generalized and complex partial seizures in a pediatric cohort of presurgical patients, confirming that postictal sympathovagal imbalance was more affected after tonic–clonic seizures and correlated with duration of EEG suppression.[36] Although several clinical studies have investigated the effects of focal seizures on ictal or postictal HRV parameters in heterogeneous study setups retarding, for example, age, seizure type, localization and lateralization of epilepsy, and HRV analysis, only very few ictal HRV data from newly diagnosed and untreated temporal lobe epilepsy have been described. In this context, our data appear to confirm the occurrence of ictal and postictal ANS dysregulation that was previously observed in drug-resistant presurgical samples.[37]

Effects of lateralization of TLE on HRV parameters

When analyzing the effect of side/lateralization of the epileptic focus, we saw a decreased vagal tone in patients with left-sided epilepsy when compared to patients with right-sided epilepsy in basal condition, as estimated through CVI. Although the cortical control of ictal cardiovascular response remains controversial,[12,24] several different mechanisms are probably involved in this phenomenon (i.e., lat-

Table 4. Differences in HRV metrics during each condition: lateralization effects (mean ± SD)

HRV metrics	R INT	L INT	p	R PRE	L PRE	p	R ICT	L ICT	p	R POST	L POST	p
LF (s^2)	1.03 ± 1.13	0.32 ± 0.35	N.S.	0.39 ± 0.1	1.56 ± 2.06	N.S.	2.04 ± 4.07	3.8 ± 4.11	N.S.	1.9 ± 2.36	2 ± 3.08	N.S.
HF (s^2)	0.77 ± 0.73	0.39 ± 0.6	N.S.	0.3 ± 0.17	0.7 ± 0.8	N.S.	1.05 ± 1.1	1.25 ± 1.08	N.S.	0.57 ± 0.59	1.12 ± 1.37	N.S.
LF/HF	1.44 ± 0.7	1.09 ± 0.45	N.S.	1.93 ± 0.17	2.06 ± 0.74	N.S.	2.65 ± 0.85	2.7 ± 0.7	N.S.	2.05 ± 0.8	2.54 ± 0.48	N.S.
RRI (s)	0.79 ± 0.08	0.86 ± 0.09	N.S.	0.84 ± 0.05	0.82 ± 0.05	N.S.	0.71 ± 0.07	0.75 ± 0.10	N.S.	0.75 ± 0.06	0.78 ± 0.1	N.S.
CSI	7.39 ± 2.7	6.9 ± 2.38	N.S.	8.5 ± 2.29	9.4 ± 43.8	N.S.	11.4 ± 6	13.9 ± 5.27	N.S.	10.7 ± 5.2	10.05 ± 2.5	N.S.
CVI	3.6 ± 0.57	3.24 ± 0.33	0.03	3.16 ± 0.2	3.27 ± 0.34	N.S.	3.47 ± 0.35	3.47 ± 0.38	N.S.	3.42 ± 0.34	3.26 ± 0.31	N.S.
RMSSD (s)	0.12 ± 0.09	0.08 ± 0.04	N.S.	0.05 ± 0.03	0.07 ± 0.04	N.S.	0.08 ± 0.05	0.07 ± 0.04	N.S.	0.07 ± 0.04	0.06 ± 0.02	N.S.
SDNN (s)	0.03 ± 0.01	0.02 ± 0.01	N.S.	0.02 ± 0.01	0.02 ± 0.01	N.S.	0.03 ± 0.01	0.05 ± 0.02	N.S.	0.03 ± 0.02	0.026 ± 0.09	N.S.
ApEn	0.51 ± 0.07	0.53 ± 0.05	N.S.	0.46 ± 0.04	0.5 ± 0.11	N.S.	0.36 ± 0.12	0.32 ± 0.14	N.S.	0.41 ± 0.08	0.47 ± 0.07	N.S.

N.S., not significant. Level of significance $p < 0.05$.

eralization of seizure onset, pattern of seizure spread and secondary generalization, and hand dominance).[38–40] Given that the pharmacologic inactivation of the right hemisphere or electrical stimulation of the left side leads predominately to a cardiodepressive response, whereas left-sided inactivation or right-sided stimulation results in an increased heart rate,[41,42] a lateralization basis of ANS regulation has long been suspected. In this study, we found evidence for an asymmetric ANS drive in TLE seizures. In left-sided TLE we observed a higher ictal vagal tone when compared to the basal state, whereas in right-sided TLE we observed a lower vagal tone in PRE versus all states, as measured by CVI. Despite the small sample size evaluated in our study, these findings are consistent with the presumed asymmetric representation of autonomic function.[29,43–45] Therefore, in patients with untreated newly diagnosed left TLE, pathology may be associated with a periictal autonomic dysfunction characterized by lower vagal tone and consequently a sympathetic predominance, as previously reported in chronic epilepsy.[7,40]

Study limitations and extensions

We recognize the following limitations of our study. Because several patients had seizures without alteration of awareness, we cannot exclude that this may have impacted HRV analysis. However, the aim of our study was to investigate temporal lobe seizures as opposed to a specific seizure population. In addition, given that in order to avoid ECG artifacts (which would deteriorate the quality of R peak detection) we selected only temporal seizures without movement artifacts, this may represent a potential selection bias in our patient population. Furthermore, because in a few patients two seizures were included, in principle we cannot exclude an underestimation of within-subject variance in our statistical analysis. However, our study was performed in newly diagnosed untreated patients affected by TLE, lacking confounding factors such as AEDs (which potentially affect ANS activity), drug-resistance, and long disease duration. Although a comparison with a group of long-lasting/drug-resistant patients would be needed to determine whether our observations are specific to the characteristics of this population, our results appear to confirm an early effect of temporal seizures on ANS activity without a full recovery in the postictal state. The putative early involvement of ANS in TLE seizures suggested by our study should be confirmed in larger patient studies and could play a potential role in designing additional early biomarkers for estimating the risk of SUDEP.

Conclusions

Our preliminary data support the hypothesis of an early involvement of ANS in untreated patients with TLE. We posit that HRV analysis may aid in recognizing seizure

onset and also in demonstrating an early impairment of ANS function in TLE.

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Disclosure

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References

1. Blumhardt LD, Smith PE, Owen L. Electrocardiographic accompaniments of temporal lobe epileptic seizures. *Lancet* 1986;1:1051–1056.
2. Massetani R, Strata G, Galli R, et al. Alteration of cardiac function in patients with temporal lobe epilepsy: different roles of EEG-ECG monitoring and spectral analysis of RR variability. *Epilepsia* 1997;38:363–369.
3. Ansakorpi H, Korpelainen JT, Huikuri HV, et al. Heart rate dynamics in refractory and well controlled temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry* 2002;72:26–30.
4. Tomson T, Ericson M, Ihrman C, et al. Heart rate variability in patients with epilepsy. *Epilepsy Res* 1998;30:77–83.
5. Harnod T, Yang CC, Hsin YL, et al. Heart rate variability in children with refractory generalized epilepsy. *Seizure* 2008;17:297–301.
6. Shobha N, Satishchandra P, Sathyaprabha T, et al. A study of interictal cardiac autonomic functions in patients with refractory complex partial epilepsy secondary to medial lobe pathology: before and after surgery. *Neurol Asia* 2007;12:69–80.
7. Evrengul H, Tanriverdi H, Dursunoglu D, et al. Time and frequency domain analyses of heart rate variability in patients with epilepsy. *Epilepsy Res* 2005;63:131–139.
8. Dutsch M, Hilz MJ, Devinsky O. Impaired baroreflex function in temporal lobe epilepsy. *J Neurol* 2006;253:1300–1308.
9. Persson H, Ericson M, Tomson T. Heart rate variability in patients with untreated epilepsy. *Seizure* 2007;16:504–508.
10. Zijlmans M, Flanagan D, Gotman J. Heart rate changes and ECG abnormalities during epileptic seizures: prevalence and definition of an objective clinical sign. *Epilepsia* 2002;43:847–854.
11. Leutmezer F, Schernthaner C, Lurger S, et al. Electrocardiographic changes at the onset of epileptic seizures. *Epilepsia* 2003;44:348–354.
12. Britton JW, Ghearing GR, Benarroch EE, et al. The ictal bradycardia syndrome: localization and lateralization. *Epilepsia* 2006;47:737–744.
13. Devinsky O. Effects of seizures on autonomic and cardiovascular function. *Epilepsy Curr* 2004;4:43–46.
14. Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. *Lancet Neurol* 2008;7:1021–1031.
15. Shorvon S, Tomson T. Sudden unexpected death in epilepsy. *Lancet* 2011;378:2028–2038.
16. Ronkainen E, Ansakorpi H, Huikuri HV, et al. Suppressed circadian heart rate dynamics in temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry* 2005;76:1382–1386.
17. Ansakorpi H, Korpelainen JT, Tanskanen P, et al. Cardiovascular regulation and hippocampal sclerosis. *Epilepsia* 2004;45:933–939.
18. Engel J Jr. International league against E. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. *Epilepsia* 2001;42:796–803.
19. Cardiology TFotESo, Cardiology TFotESo, The North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 1996;93:1043–1065.
20. Mendez MO, Bianchi AM, Montano N, et al. On arousal from sleep: time-frequency analysis. *Med Biol Eng Comput* 2008;46:341–351.
21. Karemaker JM. Autonomic integration: the physiological basis of cardiovascular variability. *J Physiol* 1999;517(Pt 2):316.
22. Toichi M, Sugiura T, Murai T, et al. A new method of assessing cardiac autonomic function and its comparison with spectral analysis and coefficient of variation of R-R interval. *J Auton Nerv Syst* 1997;62:79–84.
23. Ponnusamy A, Marques JL, Reuber M. Comparison of heart rate variability parameters during complex partial seizures and psychogenic nonepileptic seizures. *Epilepsia* 2012;53:1314–1321.
24. Sevcencu C, Struijk JJ. Autonomic alterations and cardiac changes in epilepsy. *Epilepsia* 2010;51:725–737.
25. Toschi N, Welt T, Guerrisi M, et al. Transcranial magnetic stimulation in heterogeneous brain tissue: clinical impact on focality, reproducibility and true sham stimulation. *J Psychiatr Res* 2009;43:255–264.
26. Toschi N, Welt T, Guerrisi M, et al. A reconstruction of the conductive phenomena elicited by transcranial magnetic stimulation in heterogeneous brain tissue. *Phys Med* 2008;24:80–86.
27. Hsu WY, Kuo YF, Liao KK, et al. Widespread inter-ictal excitability changes in patients with temporal lobe epilepsy: a TMS/MEG study. *Epilepsy Res* 2015;111:61–71.
28. Badawy RA, Vogrin SJ, Lai A, et al. The cortical excitability profile of temporal lobe epilepsy. *Epilepsia* 2013;54:1942–1949.
29. Lotufo PA, Valiengo L, Bensenor IM, et al. A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs. *Epilepsia* 2012;53:272–282.
30. Jeppesen J, Beniczky S, Fuglsang-Frederiksen A, et al. Detection of epileptic-seizures by means of power spectrum analysis of heart rate variability: a pilot study. *Technol Health Care* 2010;18:417–426.
31. Hohnloser SH, Klingenheben T, Vandeloo A, et al. Reflex versus tonic vagal activity as a prognostic parameter in patients with sustained ventricular-tachycardia or ventricular-fibrillation. *Circulation* 1994;89:1068–1073.
32. Luthar SS, Cicchetti D, Becker B. The construct of resilience: a critical evaluation and guidelines for future work. Child Dev. 2000;71:543–562.
33. DeGiorgio CM, Miller P, Meymandi S, et al. RMSSD, a measure of vagus-mediated heart rate variability, is associated with risk factors for SUDEP: the SUDEP-7 Inventory. *Epilepsy Behav* 2010;19:78–81.
34. Surges R, Adjei P, Kallis C, et al. Pathologic cardiac repolarization in pharmacoresistant epilepsy and its potential role in sudden unexpected death in epilepsy: a case–control study. *Epilepsia* 2010;51:233–242.
35. Toth V, Hejjel L, Fogarasi A, et al. Periictal heart rate variability analysis suggests long-term postictal autonomic disturbance in epilepsy. *Eur J Neurol* 2010;17:780–787.
36. Poh M-Z, Loddenkemper T, Reinsberger C, et al. Autonomic changes with seizures correlate with postictal EEG suppression. *Neurology* 2012;78:1868–1876.
37. Eggleston KS, Olin BD, Fisher RS. Ictal tachycardia: the head–heart connection. *Seizure* 2014;23:496–505.
38. Jallon P. Epilepsy and the heart. *Rev Neurol (Paris)* 1997;153:173–184.
39. Tinuper P, Bisulli F, Cerullo A, et al. Ictal bradycardia in partial epileptic seizures: autonomic investigation in three cases and literature review. *Brain* 2001;124:2361–2371.
40. Adjei P, Surges R, Scott CA, et al. Do subclinical electrographic seizure patterns affect heart rate and its variability? *Epilepsy Res* 2009;87:281–285.
41. Yoon BW, Morillo CA, Cechetto DF, et al. Cerebral hemispheric lateralization in cardiac autonomic control. *Arch Neurol* 1997;54:741–744.
42. Panchani J, Adjei P, Henneberger C, et al. Asymmetric hemispheric representation of periictal heart rate modulation is individually lateralised. *Epileptic Disord* 2011;13:172–176.
43. Oppenheimer SM, Gelb A, Girvin JP, et al. Cardiovascular effects of human insular cortex stimulation. *Neurology* 1992;42:1727–1732.
44. Swartz CM, Abrams R, Lane RD, et al. Heart-rate differences between right and left unilateral electroconvulsive-therapy. *J Neurol Neurosurg Psychiatry* 1994;57:97–99.
45. Surges R, Jordan A, Elger CE. Ictal modulation of cardiac repolarization, but not of heart rate, is lateralized in mesial temporal lobe epilepsy. *PLoS ONE* 2013;31;8:e64765.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Clinical and electroencephalographic features of right and left temporal seizures.

Table S2. Differences in HRV metrics—left temporal epilepsy.

Table S3. Differences in HRV metrics—right temporal epilepsy.