Received: 1 March 2020 | Accepted: 5 March 2020

DOI: 10.1111/epi.16491

Epilepsia®

SUPPLEMENT ARTICLE

Peri-ictal heart rate variability parameters as surrogate markers of seizure severity

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Funding information
Lundbeck Foundation; Health Research Fund of Central Denmark Region; Juhl Family Foundation; Swiss National Science Fund/Div3, Grant/Award Number: # and 320030-179240; International Federation of Clinical Neurophysiology

Abstract

This study aims at defining objective parameters reflecting the severity of peri-ictal autonomic changes and their relation to post-ictal generalized electroencephalography (EEG) suppression (PGES), with the view that such changes could be detected by wearable seizure detection systems and prove useful to assess the risk of sudden unexpected death in epilepsy (SUDEP). To this purpose, we assessed peri-ictal changes in heart rate variability (HRV) and correlated them with seizure duration, intensity of electromyography-based ictal muscle activity, and presence and duration of post-ictal generalized EEG suppression (PGES). We evaluated 75 motor seizures from 40 patients, including 61 generalized tonic-clonic seizures (GTCS) and 14 other major motor seizure types. For all major motor seizures, HRV measurements demonstrated a significantly decreased parasympathetic activity and increased sympathetic activity in the post-ictal period. The post-ictal increased sympathetic activity was significantly higher for GTCS as compared with non-GTCS. The degree of peri-ictal decreased parasympathetic activity and increased sympathetic activity was associated with longer PGES (>20 s), longer seizure duration, and greater intensity of ictal muscle activity. Mean post-ictal heart rate (HR) was an independent predictor of PGES duration, seizure duration, and intensity of ictal muscle contraction. Our results indicate that peri-ictal changes in HRV are potential biomarkers of major motor seizure severity.

KEYWORDS

automatic quantitative EMG (qEMG), heart rate variability (HRV), post-ictal generalized EEG suppression (PGES), seizure severity, SUDEP

1 | INTRODUCTION

Thanks to the development of wearable seizure detection devices, one might now envision using such devices to also characterize and quantify various aspects of seizure burden, beyond seizure frequency, with the view to predict and prevent morbidity and mortality. For instance, distinguishing generalized tonic-clonic seizure (GTCS) from other major motor seizures is likely to help assess the risk of sudden unexpected death in epilepsy (SUDEP). GTCS subtypes characterized by distinct semiological features and incidence of post-ictal generalized EEG suppression (PGES) have also

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been recognized, and could also help predict the risk of SUDEP. Other data suggest a relationship between SUDEP and seizure severity.[1] In current clinical practice, however, information on seizure severity is usually limited to qualitative self-reports by the patients or observation by family or caregivers. Furthermore, many seizures are overlooked.[2,3]

Peri-ictal autonomic changes are likely to play an important role in the mechanisms of SUDEP[1,4] and were found to be effective biomarkers for automated seizure detection.[5,6] Accordingly, in this explorative study, we aimed at testing whether heart rate variability (HRV) parameters could provide reliable markers of seizure severity that could later be implemented into wearable devices. We used as gold standards for seizure severity the seizure type (GTCS vs other major motor seizures), duration of seizures, duration of PGES, and intensity of ictal muscle activity determined from quantitative electromyography.

Key Points

- We compared peri-ictal heart rate variability changes with post-ictal generalized electroencephalography (EEG) suppression and with intensity of muscle activation.
- We found post-ictal increase in sympathetic activity and decrease in parasympathetic activity.
- The peri-ictal heart rate variability (HRV) parameters were correlated with seizure severity, expressed as seizure duration, intensity of muscle activation, and post-ictal generalized EEG suppression (PGES).
- Post-ictal HR mean was an independent predictor of PGES duration, seizure duration, and the intensity of ictal muscle activation.

2 | METHODS

2.1 | Patients and recordings

We have retrospectively analyzed video-EEG recordings of 40 consecutive patients (24 male, 16 female; age: 1-62 years, mean: 32.35 years, median: 30.5 years) with 75 major motor convulsive seizures (CS) from the epilepsy monitoring unit of the Danish Epilepsy Centre. We selected patients older than 1 year who had at least one CS during the monitoring. Seizures were classified by two of the authors (SB and PR) into generalized tonic-clonic seizures (GTCS; including focal to bilateral seizures) and other major motor seizures (non-GTCS) including bilateral, asymmetric focal motor seizures, and tonic seizures.

2.2 | HRV analysis

The electrocardiography (ECG) recordings were retrospectively analyzed for R-peak detection during 10-min pre-ictal periods (immediately preceding the seizures) and 10-min post-ictal periods (immediately after seizure offset). The ictal epochs were typically contaminated by muscle artifacts, making R-peak detection unreliable. Recordings were excluded from analysis when: (a) there was a discontinuation of the recording in the 10-min pre-ictal period, or (b) artifacts or very small amplitude R-peak made reliable R-peak detection impossible. Recovery of reliable R-peak detection was possible in the pre-ictal 10-min period in 43 seizures (30 patients) and in the post-ictal 10-min period in 32 seizures (21 patients). ECG was recorded as part of the polygraphic array using lead I or lead II with a 256, 500, or 512 Hz sample rate. Arrhythmias (except for the peri-ictal tachycardia) did not occur in our patients. EEG seizure-onset and seizure-offset time was determined by experts with experience in evaluating video-EEG recordings (SB and PR). Interictal ECG data were randomly chosen from available daytime recordings where no artifacts or discontinuation of the recording in the 10-min period were present, and no seizures were recorded within at least 12 h of the analyzed period.

The R-peak detection was subsequently done with a custom-made, high-pass-filtered peak-detection program (developed in LabVIEW 2011, National Instruments), where visual editing ensured that all R-peaks were selected and false-detected peaks were deleted. The editing was performed by an experienced analyst (JJ). If necessary, a second R-R interval inspection was made thereafter, with restoration and deletion of very small artifacts of the R-R intervals. However, if this restoration exceeded a total of 3 s, the recording was discarded.

The HRV time-domain parameter, root mean square of the successive differences (RMSSD) was computed for the 10-min pre-ictal and post-ictal periods and for the 10-min interictal awake and sleep periods, together with the nonlinear parameter Cardiac Sympathetic Index (CSI), which was calculated using the geometric Lorenz plot method, as described in detail elsewhere.[7] For frequency analysis of HRV, the R-R intervals were first interpolated and resampled with 10 Hz using cubic Hermite interpolation to ensure even sampling rate of the R-R wave signal. Fast Fourier transformation analysis was then performed based on a 595s Hanning window for 10-min epochs for the inter-ictal, pre-ictal, and post-ictal analysis. The power spectrum density of low frequency (LF) (0.04-0.15 Hz) and high frequency (HF) (0.15-0.4 Hz) was derived, and the ratio LF/HF was obtained. HR mean was calculated as the mean heart rate of the 10-min windows. HF and RMSSD

TABLE 1 Pre-ictal and post-ictal heart rate variability (all parameters are calculated normalized to the interictal values) (Wilcoxon signed-rank test)

	GTCS seizures					non-GTCS seizures				
HRV parameters	**Median pre-ictal**	**[25%-75%] pre-ictal**	**Median post-ictal**	**[25%-75%] post-ictal**	***P***	**Median pre-ictal**	**[25%-75%] pre-ictal**	**Median post-ictal**	**[25%-75%] post-ictal**	***P***
HR mean	0.93	[0.91-1.02]	1.58	[1.51-1.66]	.001*	0.87	[0.83-1.02]	1.26	[1.06-1.73]	.017*
HF power	1.11	[0.97-1.91]	0.06	[0.01-0.46]	.004*	1.88	[1.27-4.03]	0.37	[0.07-0.95]	.036*
RMSSD	0.95	[0.65-1.45]	0.19	[0.14-0.71]	.007*	1.25	[0.80-1.84]	0.97	[0.33-1.71]	.401
LF/HF	0.56	[0.34-0.80]	1.58	[0.40-3.45]	.013*	0.43	[0.27-0.73]	0.93	[0.49-2.28]	.123
CSI	0.93	[0.72-1.32]	4.71	[2.68-5.91]	.002*	0.89	[0.69-0.93]	1.03	[0.77-2.79]	.327

*Statistically significant ($P < .05$)

CSI: cardiac sympathetic index; GTCS: Generalized tonic-clonic seizures, including focal to bilateral tonic-clonic seizures; HF: high frequency; HR: heart rate; HRV: heart rate variability; LF: low frequency; RMSSD: root mean square of successive differences.

were considered parameters reflecting parasympathetic activity, LF/HF ratio and CSI were considered indicators of sympathetic activity, and HR mean was considered a mixed parasympathetic and sympathetic parameter. To compensate for the large inter-individual variability of the HRV, we normalized each pre-ictal and post-ictal measurements by dividing them with the corresponding interictal measurement of each patient.

2.3 | Seizure severity analysis

We used the following surrogate markers of seizure severity: PGES duration, seizure type (GTCS vs non-GTCS), seizure duration, and intensity of ictal muscle activation. PGES was assessed by two independent visual assessments (PR and AAA), blinded to seizure type and patient status. PGES was defined as a generalized attenuation of EEG activity starting immediately or within the first 30 s after an ictal EEG pattern has stopped, with a duration of ≥1 s and an amplitude of <10 μV.[8,9] Considering that the 20 s threshold indicated a higher risk of SUDEP in previous studies,[9,10] we also divided our lot into two groups (PGES duration <20 and ≥20 s).

We measured seizure duration and the intensity of ictal muscle activity using quantitative analysis of surface electromyography (EMG). Electrodes (silver/silver chloride 9-mm surface electrodes) were placed on the deltoid muscles, on both sides, in addition to the standard EEG electrodes. The active electrodes were placed on the midpoints of the muscle bellies. The reference electrodes were placed on the acromioclavicular joint, proximal to the insertion of the deltoid muscle. EMG was sampled with a frequency of 1024 Hz with an anti-aliasing filter of 512 Hz. Next, the EMG signals were analyzed in MATLAB with blinding to all other data. Seizure duration was automatically calculated from the quantitative EMG (qEMG) data using a previously validated method.[11,12] We also calculated the number of sliding windows with baseline zero crossings above the threshold (ZC above) as a biomarker of seizure intensity.

2.4 | Statistical analysis

Statistical analysis was performed with SPSS version 19 software. We calculated means and standard deviations (SDs) for PGES duration and qEMG parameters. We determined the correlations between the nonlinear variables using Spearman's rho. We performed two-sided Wilcoxon signed-rank test to compare pre-ictal and post-ictal values, as well as the Mann-Whitney *U* test or paired-sample *t* test where appropriate for the comparison between seizure types. Finally, we used stepwise multiple regression analysis to identify

which independent HRV parameters significantly predict PGES duration (absolute value and categories), total seizure duration, and ZC-above. We used a level of statistical significance of <.05.

3 | RESULTS

Among the 40 consecutive patients included in this study, 30 had GTCS and 11 non-GTCS, with one patient presenting both types of major motor seizures. Among the 75 collected seizures, 61 were GTCS and 14 non-GTCS, including three opercular seizures involving at least one upper limb, six bilateral asymmetric focal motor seizures, and five tonic focal motor seizures.

GTCS differed from non-GTCS in terms of total seizure duration (64.12 ± 20.45 s vs 37.59 ± 47.56 s, $P = .060$), PGES duration (33.24 ± 22.03 s vs 3.03 ± 7.17 s, $P < .001$), and mean ZC-above (39.80 ± 24.36 vs 4.86 ± 12.35, $P < .001$).

In GTCS we observed a significant post-ictal increase in sympathetic activity (increase in CSI and LF/HF ratio) and decrease in parasympathetic activity (HF power and RMSSD). In addition, there was a marked increase in HR mean (combination of increased sympathetic and decreased parasympathetic activity). In non-GTCS, there was a significant post-ictal increase in HR mean and decrease in HF power. However, GTCS had a significantly higher increase in HR mean ($P < .05$) and in CSI ($P < .05$) than non-GTCS, suggesting that post-ictal sympathetic activation is more pronounced in GTCS (Table 1).

We found that the post-ictal increase in HR mean and pre-ictal decrease in HF power correlated with prolonged (≥20 s) PGES and with long seizure duration (Table 2). Moreover, pre-ictal and post-ictal increase in HR mean, pre-ictal decrease in HF power, and pre-ictal increase in LF/HF ratio correlated with greater ictal muscle activity (Table 2).

Stepwise linear regression analysis showed that post-ictal HR mean was an independent predictor of absolute PGES duration ($P = .015$; $r^2 = .272$), long PGES category (≥20 s; $P = .009$; $r^2 = .305$), total seizure duration ($P < .001$; $r^2 = .564$) and ZC-above ($P = .047$; $r^2 = .130$). The latter was also independently predicted by pre-ictal LF/HF ratio ($P = .001$; $r^2 = .241$).

4 | DISCUSSION

According to our hypothesis, we found that several peri-ictal HRV parameters can be used as surrogates of major motor seizure severity. In particular, post-ictal HR mean was associated with all four markers of seizure severity considered in this study, that is, GTCS vs other seizure types, total seizure duration, intensity of muscle activation, and PGES duration.

The choice of the above markers as gold standard of major motor seizure severity ought to be discussed. There is compelling evidence that GTCS is associated with higher risks of SUDEP than other major motor seizures.[4,13] PGES has also been associated with a greater risk of SUDEP, but this finding remains disputed.[14] However, regardless of this association, PGES, total seizure duration, and intensity of ictal muscle activity offer objective assessments of the intensity of motor seizures, which one would like to quantify to best characterize and manage people with such seizures.

Many previous studies investigated HRV in patients with epilepsy.[6] Most studies analyzed interictal HRV and found a shift in autonomic balance toward sympathetic dominance.[6] In contrast, Tomson et. al.[15] found a decreased interictal sympathetic tone in patients with epilepsy vs healthy controls, but some of the included patients were

TABLE 2 Correlations between peri-ictal HRV and seizure severity parameters (Spearman's)

	Long PGES (≥ 20 s)		Total seizure duration		ZC-above	
HRV parameters	***R***	***P***	***R***	***P***	***r***	***P***
HR-mean pre-ictal	.055	.729	.188	.233	.344	.026*
HF power pre-ictal	−.366	.017*	−.331	.032*	−.330	.033*
RMSSD pre-ictal	−.201	.203	−.281	*.072*	−.195	.216
LF/HF pre-ictal	.083	.603	.126	.425	.457	.002*
CSI pre-ictal	.161	.308	.184	.245	.225	.152
HR-mean post-ictal	.395	.028*	.478	.007*	.433	.015*
HF power post-ictal	−.183	.325	−.294	.108	−.162	.385
RMSSD post-ictal	−.270	.141	−.226	.222	−.148	.428
LF/HF post-ictal	.183	.325	.198	.287	.319	.080
CSI post-ictal	.248	.178	.122	.515	.123	.511

*Statistically significant ($P < .05$).

not treated, epilepsy patients had either focal temporal epilepsy or juvenile myoclonic epilepsy, and there were no comparisons of HRV parameters between the two epilepsy groups. Previous studies have also linked interictal RMSSD changes to SUDEP risk in patients with both focal and generalized epilepsy.[1]

In our study, we focused on peri-ictal (ie, pre-ictal and post-ictal) HRV changes, since ultra-long-term recordings with seizure-detecting wearable devices can provide such measurements. We used the interictal values only to normalize the peri-ictal HRV, to compensate for the huge inter-subject variability of HRV, which is an important source of potential bias in many studies on HRV. Results of previous studies on peri-ictal HRV are not completely consistent.[6] However, most studies suggest an ictal and post-ictal increase in sympathetic activity and post-ictal decrease in parasympathetic activity.[6] Our results confirm these changes. We found that in GTCS there is a post-ictal increase in sympathetic activity (CSI and LF/HF ratio) and a decrease in parasympathetic activity (HF power), in agreement with the studies of Poh et al[16] and Lamberts et al.[17] A trend of post-ictal decrease in RMSSD was found by Esmaeili et al,[18] but it was not statistically significant. The study of Jaychandran et al analyzed peri-ictal HRV changes, but in contrast to our study did not include patients with generalized convulsions.[19] Some of our findings are concordant with this study (post-ictal decrease in parasympathetic HRV), whereas others are discordant (they did not find post-ictal increase in sympathetic HRV).[19]

The correlation between PGES and post-ictal HRV reported herein is controversial, probably due to the considerable methodological differences and the heterogeneity of the studied populations. In agreement with our own findings, two studies[16,20] showed that PGES was correlated with post-ictal decrease in parasympathetic activity (HF power[16] and RMSSD[20]). In contrast, two other series failed to replicate these results,[17,21] while another study found that GTCS with PGES was associated with a smaller decrease in post-ictal parasympathetic activity (RMSSD)[22] than GTCS without PGES. We also found a significant correlation between PGES and pre-ictal decrease in parasympathetic activity (HF power) that has not been reported previously.

The more pronounced change in HRV that we observed in GTCS as compared with non-GTCS is similar to that reported in previous studies,[16,18] although the latter studies compared GTCS or bilateral convulsive seizures with focal seizures, not focal major motor seizures as in this study. We also found marked post-ictal increase in CSI, which has not been explored previously.

Our findings that post-ictal increase in HR mean and pre-ictal decrease in HF power correlate with total seizure duration was also not observed in previous studies.[16,17,20] We used an objective method for determining seizure duration, based on an EMG algorithm, which eliminated the component of subjectivity in measuring seizure duration.

The relationship between HRV and the intensity of ictal muscle activity as quantified by ZC above has not been studied before. Of interest, this activity correlated with several HRV parameters including peri-ictal increase in HR mean, pre-ictal increase in sympathetic activity (LF/HF ratio), and decrease in parasympathetic activity (HF power), suggesting a robust link between these biomarkers.

A limitation of our study is that we have not recorded oxygen saturation. Hypoxemia might be an important confounder.[23] Another limitation is that we did not have a sufficient number of patients to investigate the possible role of the seizure-onset zone (for patients with focal-to-bilateral tonic-clonic seizures), as compared with patients with primary GTCS. This is an interesting topic for further investigation.

The major, novel findings of our study are the following: Significant correlation between pre-ictal decrease in parasympathetic activity (HF power) and PGES; significant correlations between peri-ictal HRV changes, seizure duration and intensity of ictal muscle activations; post-ictal HR mean is an independent predictor of PGES; and seizure duration and intensity of ictal muscle activation.

In conclusion, we found that peri-ictal HRV measurements might be used to indirectly quantify several aspects of major motor seizure severity, including the type of motor seizure, total seizure duration, PGES duration, and intensity of ictal muscle activity. Now that U.S. Food and Drug Administration (FDA)–approved and CE-marked (certificate in the European Union for medical use) wearable devices are available to reliably detect GTCS, it appears desirable to use the same or future devices to further characterize the severity of the detected seizures. HR is one of the most used and easily captured biosignals by wearable devices, making the implementation of automatic peri-ictal HRV in GTCS detectors a realistic short-term goal. Further studies on ultra-long-term outpatient recordings are needed to elucidate the role of HRV measurements for risk assessment and prevention of SUDEP.

ACKNOWLEDGMENTS

The research was supported by the Lundbeck Foundation, the Health Research Fund of Central Denmark Region, the Juhl Family Foundation, the Swiss National Science Fund/Div3 #320030-179240 (SEVERITY), and by a fellowship grant from the International Federation of Clinical Neurophysiology.

CONFLICTS OF INTEREST

Author IC is an employee of FORCE Technology, Copenhagen, Denmark. The remaining authors do not have any conflict of interest to disclose, related to this article. We confirm that we have read the Journal's position on issues

involved in ethical publication and affirm that this report is consistent with those guidelines.

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How to cite this article: Arbune AA, Jeppesen J, Conradsen I, Ryvlin P, Beniczky S. Peri-ictal heart rate variability parameters as surrogate markers of seizure severity. *Epilepsia*. 2020;00:1–6. https://doi.org/10.1111/epi.16491