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Article · August 2014

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Using Lorenz plot and Cardiac Sympathetic Index of heart rate variability for detecting seizures for patients with epilepsy

Jesper Jeppesen [1], Sándor Beniczky [1,2], Peter Johansen [3], Per Sidenius [4], Anders Fuglsang-Frederiksen[1]

Abstract— **Tachycardia is often seen during epileptic seizures, but it also occurs during physical exercise. In order to assess whether focal epileptic seizures can be detected by short term moving window Heart Rate Variability (HRV) analysis, we modified the geometric HRV method, Lorenz plot, to consist of only 30, 50 or 100 R-R intervals per analyzed window. From each window we calculated the longitudinal (L) and transverse (T) variability of Lorenz plot to retrieve the Cardiac Sympathetic Index (CSI) as (L/T) and "Modified CSI" (described in methods), and compared the maximum during the patient's epileptic seizures with that during the patient's own exercise and non-seizure sessions as control.**

All five analyzed patients had complex partial seizures (CPS) originating in the temporal lobe (11 seizures) during their 1-5 days long term video-EEG monitoring. All CPS with electroencephalographic correlation were selected for the HRV analysis. The CSI and Modified CSI were correspondently calculated after each heart beat depicting the prior 30, 50 and 100 R-R intervals at the time. CSI (30, 50 and 100) and Modified CSI (100) showed a higher maximum peak during seizures than exercise/non-seizure (121-296%) for 4 of the 5 patients within 4 seconds before till 60 seconds after seizure onset time even though exercise maximum HR exceeded that of the seizures. The results indicate a detectable, sudden and inordinate shift towards sympathetic overdrive in the sympathovagal balance of the autonomic nervous system just around seizure-onset for certain patients. This new modified moving window Lorenz plot method seems promising way of constructing a portable ECG-based epilepsy alarm for certain patients with epilepsy who needs aid during seizure.

I. Introduction

The random occurrence and unpredictability of seizures is of the most distressful and disabling issues affecting patients with epilepsy and their families. Unattended seizures can furthermore lead to serious injuries and also increase the risk of sudden unexpected death in epilepsy (SUDEP) [1]. A reliable alarm system notifying relatives and medical staff of a focal seizure, which could later generalize to a more severe secondary generalized tonic-clonic seizure (SGTCS) would therefore be a great asset for patients with epilepsy and their families [2].

Attempts of developing a portable, non-invasive epilepsy alarm system for generalized tonic-clonic seizures have already been done with electromyography (EMG) [3], electrodermal response [4] and accelerometry [5] but still a warning system for focal seizures and SGTCS prior to the clonic phase have not been successful. Heart rate and Heart rate variability changes before and just after seizure onset have been reported in multiple studies, but no clear-cut method to a portable seizure alarm system have been made so far [6]–[10]. The heart rate tachycardia accompanying most seizures has not yet been distinguished from regular exercise tachycardia. Therefore our aim for this study was to search for short term heart rate variability algorithms, which can distinguish the heart rate variability changes before or during seizures with those during exercise and other non-seizure periods.

II. Patients

Thirteen patients enrolled at the video-EEG long term monitoring unit for epilepsy (EMU) in Aarhus University Hospital and at the Danish Epilepsy Center, Dianalund, Denmark from September 2011 to June 2012 signed a written agreement and participated in the study. The protocol of this study was approved by The Danish National Committee on Biomedical Research Ethics. Patients with a history of coronary heart disease, diabetes or any other known disease that might affect the autonomic nervous system were excluded, as were pregnant or nursing female patients.

All the enrolled patients completed an exercise session during the video-EEG monitoring to compare tachycardia during exercise to tachycardia during seizure. The exercise sessions were made on exercise bikes, where patients did a stepwise pulse increase of 110 beats/min for 2 minutes, 140 beats/min for 2 minutes and all-out maximum for 3 minutes.

Five of the 13 enrolled patients had epileptic seizures with EEG-correlate. These were complex partial seizures, from the temporal lobe. The electroencephalographic onset and offset of the 11 complex partial seizures was determined by trained specialists and used as time-reference for time comparison of HRV-results.

This research was supported by The Danish Council for Independent Research, Lundbeck Foundation, Health Science Aarhus University, Aase & Ejner Danielsens Fond and Brødrene Hartmann Foundation.

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978-1-4244-7929-0/14/$26.00 ©2014 IEEE

III. METHODS

A. ECG processing

The ECG was recorded using lead II (right clavicle to left lower ribs (costae)) with sampling frequency 512 Hz on the same system as the video-EEG (NicoletOne) to ensure optimal time synchronization. ECG-data from three non-seizure periods and all seizure periods (15-20 minutes pre- to 10 minutes post-seizure onset) were extracted from the NicoletOne and further processed and analyzed in custom made computer programs (developed in LabVIEW 2011, National Instruments). The three non-seizure periods consisted of:

1) The first 30 minutes daytime awake non-seizure period without artifacts +3 hours before the first seizure
2) A nighttime non-seizure period from 2 am – 2.30 am the night before the first seizure (if patient was awake the first following sleep period was used)
3) A 18-30 minute period containing the exercise-session

The ECG-data was prepared for R-peak detection by using 5-15 Hz finite impulse response high-pass filter to remove baseline drift and artifacts. The R-peak detection was subsequently done using peak-detection, where manual editing ensured all R-peak were selected and false detected peaks were deleted. The editing was performed by an experienced user.

B. Lorenz plot analysis

Lorenz plot (or Poincare plot) is done by plotting each R-R interval time length (I_k) against the following R-R interval time length (I_k,I_{k+1}) for a limited number of R-R intervals (k) (Fig. 1). Calculation of the standard deviations for the transverse direction (Sd1) which is vertical to the I_k=I_{k+1} line (1) and the longitudinal direction (Sd2) which is parallel to the I_k=I_{k+1} line (2) (Fig. 1) is done with the following equations:

$$Sd1 = \sigma\left(\frac{\sqrt{2}}{2}[(I_1 - I_2 \cdots I_k - I_{k+1})]\right);\ k = \{30;50;100\} \quad (1)$$

$$Sd2 = \sigma\left(\frac{\sqrt{2}}{2}[(I_1 - I_2 \cdots I_k - I_{k+1})]\right);\ k = \{30;50;100\} \quad (2)$$

, where k represents the three different number of R-R intervals windows (30, 50, 100) we chose for the analysis.

To approximate the visual image on the Lorenz plot, Toichi et al. [11] introduced the transverse length (T) as four times the Sd1 and the longitudinal length (L) as four times the Sd2 (Fig. 1). An estimation of the sympathetic and parasympathetic tonus from the Lorenz plot can then be given as respectively L/T for Cardiac Sympathetic Index (CSI) and $\log_{10}(L\times T)$ for Cadiac Vagal Index (CVI) [11]. Initially we found that the CSI and especially the longitudinal parameter (L) of the CSI seemed to produce a great increase during the late pre-ictal and early ictal phase of the seizures (Fig. 2A). Therefore we introduce a new mathematical approach to the Lorenz plot that emphasizes the longitudinal (L) value to a greater extend, which we have termed "Modified CSI" (L^2/T) as an alternative measure in search of seizure detection.

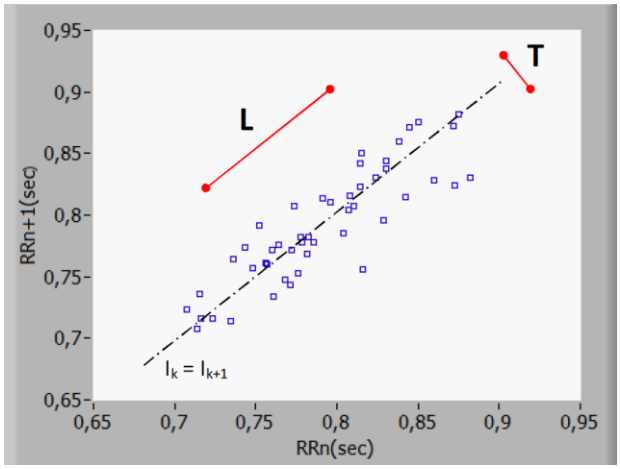
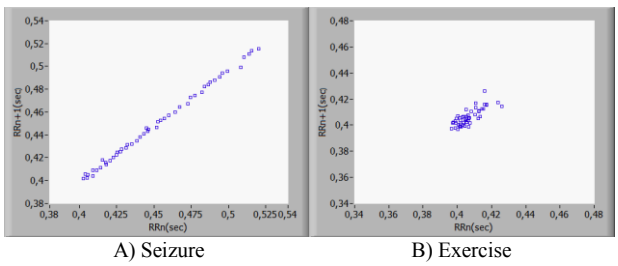


Figure 1. Lorenz plot example from non-seizure day patient 5, with 50 R-R intervals. The transverse axis (T) reflects beat-to-beat variation, while the longitudinal axis (L) reflects the overall fluctuation.

Both CSI and Modified CSI were calculated using respectively 30, 50 and 100 R-R interval moving windows (k = 30; 50; 100) with maximum overlapping for the whole 30 minute period of all the seizure and non-seizure periods. The values of CSI and Modified CSI are depicted so that the time point corresponding to each value consist of the Lorenz plot computation of the prior 30, 50 or 100 R-R intervals (see example Fig. 3). In this way the time of the calculated continuous CSI and Modified CSI correspond to the actual time the value temporally can be measured.

Maximum value of CSI and Modified CSI within 1 minute pre-seizure onset to 3 minutes post seizure onset was computed and a positive detection was regarded when this seizure maximum exceeded the maximum of all non-seizure periods for the same patient. The ratio of seizure maximum vs. non-seizure maximum was computed in order to establish the relative difference and consider reliability of the algorithms.



A) Seizure B) Exercise

Figure 2. A) Lorenz-plot from time of maximal CSI_{50} patient 5, during 2nd seizure. B) Example of Lorenz plot of patient 5 during exercise test

TABLE I. MAXIMUM CSI AND MODIFIED CSI VALUES

	Non-seizure	Seizure 1	Seizure 2	Seizure 3	Seizure 4	Seizure 5
CSI $_{30}$						
Patient 1	12.75	**20.76**	**21.20**			
Patient 2	14.03	**20.87**				
Patient 3	13.81	**29.61**				
Patient 4	21.85	16.37	20.71	19.89	**22.30**	**21.89**
Patient 5	14.32	**17.93**	**32.74**			
CSI $_{50}$						
Patient 1	12.05	**24.74**	**20.24**			
Patient 2	12.01	**26.89**				
Patient 3	14.83	**37.91**				
Patient 4	25.82	14.69	20.64	21.58	25.35	**25.97**
Patient 5	12.74	**18.74**	**36.83**			
CSI $_{100}$						
Patient 1	17.42	**21.10**	**29.10**			
Patient 2	13.92	**18.03**				
Patient 3	19.24	**47.19**				
Patient 4	20.56	8.77	**21.55**	16.52	10.92	17.62
Patient 5	15.52	**22.92**	**33.48**			
Modified CSI$_{30}$						
Patient 1	3362	2966	2470			
Patient 2	15572	10396				
Patient 3	9354	8103				
Patient 4	9881	9357	**14160**	**13663**	**11332**	9976
Patient 5	7201	3523	4173			
Modified CSI$_{50}$						
Patient 1	4427	**4848**	3749			
Patient 2	12668	**16857**				
Patient 3	6265	**15325**				
Patient 4	11388	8330	**13900**	**18195**	**20940**	**13145**
Patient 5	7679	5176	**7907**			
Modified CSI$_{100}$						
Patient 1	3552	**6417**	**9012**			
Patient 2	9304	**13430**				
Patient 3	10657	**31597**				
Patient 4	12242	3096	14675	5885	8257	9387
Patient 5	7843	**12048**	**14046**			
Max. pulse (beats/min)						
Patient 1	171	131	140			
Patient 2	149	147				
Patient 3	167	152				
Patient 4	167	105	109	138	113	123
Patient 5	168	150	157			

*Red numbers are maximum seizure-values of CSI and Modified CSI exceeding maximum non-seizure values (blue) illustrating positive detection.

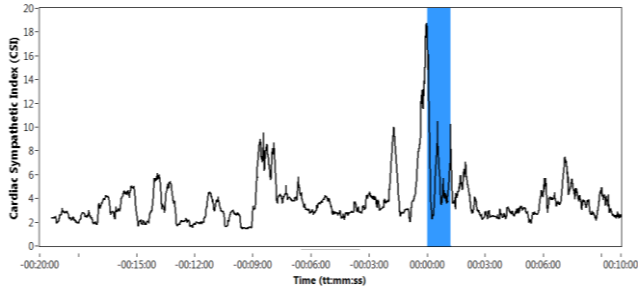


Figure 3. Cardiac Sympathetic Index (CSI) calculated using moving windows of 50 R-R intervals with 30 minutes data (patient 5, 1st seizure). Seizure-time of 103 sec. is marked with blue color.

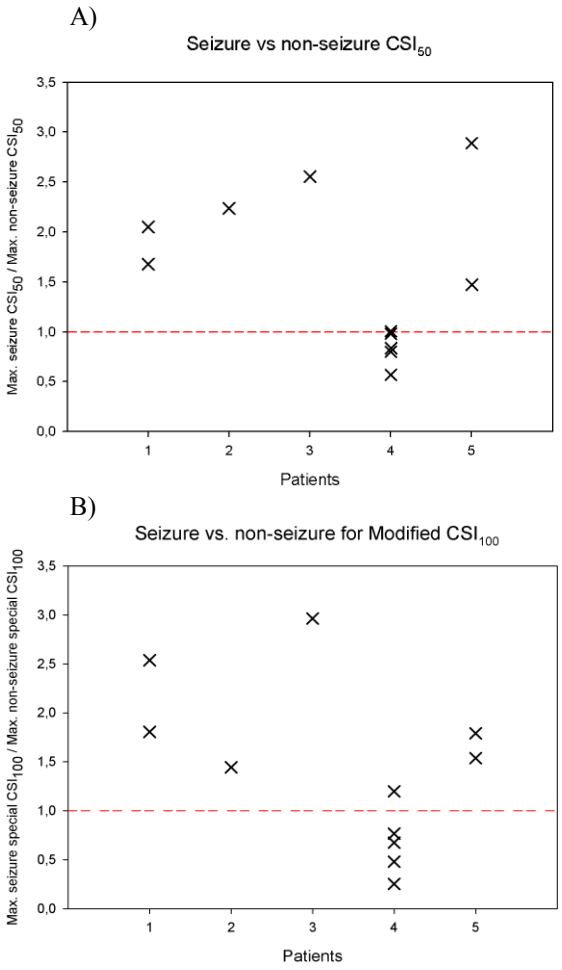


Figure 4. A) Ratio of maximum CSI_{50} seizure vs. maximum CSI_{50} non-seizure periods for all patients and seizures. B) Ratio of maximum Modified CSI_{100} seizure vs. maximum Modified CSI_{100} non-seizure periods for all patients and seizures. (red dotted line illustrates cut-off line for seizure detection).

TABLE II. SEIZURE MAX. / NON-SEIZURE MAX. FOR THE FOUR PATIENTS AND METHODS WHERE ALL SEIZURES HAD POSITIVE DETECTION.

	Patient 1, (1)	Patient 1, (2)	Patient 2, (1)	Patient 3, (1)	Patient 5, (1)	Patient 5, (2)	Range	Median
CSI $_{30}$	1.63	1.66	1.49	2.14	1.25	2.29	1.25 - 2.29	1.65
CSI $_{50}$	2.05	1.68	2.24	2.56	1.47	2.89	1.47 - 2.89	2.15
CSI $_{100}$	1.21	1.67	1.29	2.45	1.48	2.16	1.21 - 2.45	1.57
Modified CSI $_{100}$	1.81	2.54	1.44	2.96	1.54	1.79	1.44 - 2.96	1.80

IV. RESULTS

Four of the five patients had positive seizure detection for all seizures for the CSI-method using CSI_{30}, CSI_{50} and CSI_{100} and the Modified CSI-method using Modified CSI_{100} (Table 1 & 2 & Fig. 4). The four patients with positive seizure detections had individual ratio of CSI_{50} seizure maximum vs. non-seizure maximum of 1.47–2.89 (median: 2.15) (Fig. 4a & Table 2) with time of peak CSI_{50} between 2 sec. before till 40 sec. after seizure onset time (median: 8 sec. after onset) (Fig. 5). Same four patients had individual ratio of Modified CSI_{100} seizure maximum vs. non-seizure maximum of 1.44 – 2.96 (median 1.8) (Fig. 4b & Table 2) with time of peak Modified CSI_{100} between 3 - 40 seconds after seizure onset (median: 17 sec.) (Fig. 5). All patients had a higher maximum pulse during non-seizure periods (exercise) than any of their own seizures (Table 1).

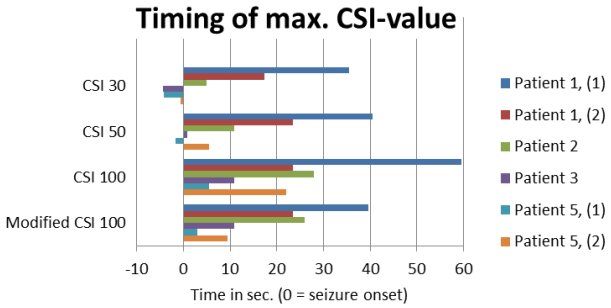


Figure 5. Time of the maximum value of CSI_{30}, CSI_{50}, CSI_{100} and Modified CSI_{100} for the four patients with positive seizure detection. Time zero is seizure onset time. Numbers in parentheses are number of seizures if more than one.

V. Discussion

Our preliminary analysis of using very short term Lorenz plot method of heart rate variability as seizure detector seems promising as four out of five patients had positive detection of seizures, when using methods: CSI_{30}, CSI_{50}, CSI_{100} and Modified CSI_{100}. In our analysis we eliminated the aspect of high individual HRV differences by comparing the HRV parameters before/during seizures of each patient with the patient's own non-seizure periods as control reference. We thereby also suggest that the best way of making and seizure detection algorithm from HRV is by setting an individual threshold for the seizure alarm, which will improve the sensitivity and specificity considerably.

A global seizure alarm system using the methods described here does not seem feasible. One patient had five seizures from which none of our algorithms could detect all of the seizures. However we suspect that relative low maximum heart rate during seizure for this patient is the main reason to why the algorithms were unsuccessful for this patient. Although our results suggest seizure detection after onset for some seizures, this can still be an important asset, when assistance is required during and after the seizures and could also serve as a potential SUDEP prevention, as supervision is associated with reduced SUDEP-risk [2].

When using only 30 to 100 R-R intervals for our Lorenz plot analysis we did not fulfill the guidelines for heart rate variability minimum time windowing [12]. We had three reasons for this: firstly, when using standard minimum of 5 minute periods for HRV analysis the seizure will in most cases not be detected until several minutes after onset, secondly the very fast evolving heart rate changes happening around seizure onset can better be detected by very short time window analysis and thirdly our main aim with the algorithms presented here is not necessarily to prove a standardized autonomic change, but instead to search for a heart rate seizure detection option. The results however still indicate a sudden and inordinate shift towards sympathetic overdrive in the sympathovagal balance of the autonomic nervous system just around seizure-onset for certain patients. Furthermore the short term Lorenz plot HRV-method seems as a promising tool of constructing an algorithm for seizure detection for specific patients with epilepsy.

VI. Conclusion

The methods of short term moving window Lorenz plot presented in this study seems promising as an easy and inexpensive way of constructing a portable ECG-based epilepsy alarm for certain patients with epilepsy who needs aid during seizure. Further studies with larger cohort of consecutive patients are needed for evaluation of the clinical usefulness of the methods presented and to determine reliability and which patient groups the detection algorithms are applicable.

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