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Comparing maximum autonomic activity of psychogenic non-epileptic seizures and epileptic seizures using heart rate variability

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ABSTRACT

Purpose: The semiology of psychogenic non-epileptic seizures (PNES) can resemble epileptic seizures, and differentiation between epileptic seizures with no EEG-correlate and PNES can be challenging even for trained experts. Therefore, there has been a search for a quantitative measure, other than EEG and semiology that could distinguish PNES from epileptic seizures. We used ECG to measure heart rate variability (HRV) in order to compare maximum autonomic activity of epileptic seizures and PNES. These comparisons could potentially serve as biomarkers for distinguishing these types of clinical episodes.
Method: Forty-nine epileptic seizures from 17 patients and 24 PNES from 7 patients with analyzable ECG were recorded during long-term video-EEG monitoring. Moving windows of 100 R–R intervals throughout each seizure were used to find maximum values of Cardiac Sympathetic Index (CSI) (sympathetic tonus) and minimum values of Cardiac Vagal Index (CVI), Root-Mean-Square-of-Successive-Differences (RMSSD) and HF-power (parasympathetic tonus). In addition, non-seizure recordings of each patient were used to compare HRV-parameters between the groups.
Results: The maximum CSI for epilepsy seizures were higher than PNES ($P = 0.015$). The minimum CVI, minimum RMSSD and HF-power did not show significant difference between epileptic seizures and PNES ($P = 0.762$; $P = 0.152$; $P = 0.818$). There were no statistical difference of non-seizure HRV-parameters between the PNES and epilepsy patients.
Conclusion: We found the maximum sympathetic activity accompanying the epileptic seizures to be higher, than that during the PNES. However, the great variation of autonomic response within both groups makes it difficult to use these HRV-measures as a sole measurement in distinguishing epileptic seizures from PNES.

1. Introduction

The electrical discharge in the brain which characterizes epileptic seizures cannot always be detected by electroencephalography (EEG) or magnetoencephalography (MEG). The semiology of psychogenic nonepileptic seizures (PNES) can resemble epileptic seizures, and differentiation between epileptic seizures and PNES can be challenging even for trained experts. Therefore, there has been a quest for a quantitative measure, other than EEG and semiology that could distinguish PNES from epileptic seizures. Especially heart rate changes and heart rate variability changes have been under investigation [1–3]. In 2002, Opherk and Hirsch found that heart rate (HR) change was significantly higher during epileptic seizures than during PNES (both convulsive and non-convulsive) [3]. However, Reinsberger et al. could not find any difference of HR change between nonconvulsive epileptic seizures and nonconvulsive PNES [1]. Therefore suggestions of using more advanced form of heart rate analysis, such as heart rate variability (HRV), in search of distinguishing PNES and epileptic seizures has recently been made [2].

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Heart rate variability (HRV) analysis is used to assess alternations of both the sympathetic and parasympathetic activity of the autonomic nervous system (ANS) [4]. Using HRV the activation of the ANS has been shown to change suddenly and markedly, towards higher sympathetic activity in the immediate pre-ictal phase and during seizures for most patients with epilepsy [5,6]. It has been suggested that this is because of the direct link of seizures to the areas in the brain connected to the ANS [7]. PNES seizures have also been shown to influence the ANS during seizures [2]. This study showed the average HRV-response of sympathetic tonus during epileptic seizures was significant higher than during PNES and the parasympathetic tonus was significant reduced during epileptic seizure in comparison with PNES [2]. However in this study, the HRV-analysis was made as an average of the whole seizure period for both epileptic seizures and for PNES. Thus, the HRV-analysis were in average 1.15 (range 1–3 min) for epileptic seizures and 2 min (range 1–4 min) in the PNES group. This difference in lengths of HRV-analyses between the groups can create a potential bias in the HRV results, when using short time HRV-analysis [4]. In earlier studies we discovered that the timing of maximum peak of sympathetic tonus [6] and the minimum of parasympathetic tonus [8] in epileptic seizures varies among patients and seizures. Some epileptic seizures even show maximum change of HRV-parameters in the pre-ictal phase [6,8]. Also heart rate changes have been shown to precede the scalp EEG changes [9,10].

Our hypothesis was that maximum values of sympathetic tonus and minimum values of parasympathetic tonus will better describe the phenomena in the ANS, since they do not depend on the duration of the events. These vales/thresholds could potentially serve as biomarkers for the specific clinical episodes. In order to find the maximum peak of sympathetic tonus (using Cardiac Sympathetic Index (CSI)) and minimum parasympathetic tonus nadir (using Cardiac Vagal Index (CVI) and Root mean square of successive differences (RMSSD)) during seizures, we therefore calculated HRV-measures with equal numbers of R–R intervals, using a moving window with 100 R–R intervals. Furthermore, we included the pre-ictal and immediate post-ictal periods of the seizures, to test our hypothesis that peaks of HRV changes during the peri-ictal period of epileptic seizures and PNES can distinguish epileptic seizures from PNES.

2. Methods

2.1. Patients

Thirty-nine patients were recruited in the period from September 2011 to December 2013, when admitted to the long term video-EEG monitoring unit (EMU) at Aarhus University Hospital, Denmark and at the Danish Epilepsy Center, Dianalund, Denmark for diagnostic reasons or pre-surgical evaluation. All patients gave written, informed consent and the study was approved by the Ethics Committee (ID M-20110107). Forty-nine epileptic seizures were recorded from 17 patients (7 right temporal lobe, 6 left temporal lobe, 4 frontal lobe) and 24 psychogenic non-epileptic seizures (PNES) were recorded from 7 patients with analyzable ECG during the monitoring.

2.2. ECG recordings and processing

The electroencephalographic and clinical onset and offset of all seizures was determined by trained specialists and used as time-reference for time comparison of HRV-results. Whichever seizure-onset came first (electroencephalographic or clinical) was chosen as seizure-onset time and whichever seizure-offset came last was chosen as seizure-offset time. The ECG was recorded using lead II (right clavicle to left lower ribs (costae)) with sampling frequency of 256 or 512 Hz on the same system as the video-EEG (NicoletOne) to ensure optimal time synchronization. The ECG-data of all the seizures (both PNES and epileptic) were extracted from 15 to 20 min before to 10 min after seizure-onset from the NicoletOne and further processed and analyzed in custom made computer programs (developed in LabVIEW 2011, National Instruments). In the LabVIEW program the raw ECG was first prepared for R-peak detection by using 5–15 Hz finite impulse response high-pass filter to remove baseline drift and artifacts. Subsequently, manual adjustable peak detection threshold was used to find the R-peaks of the ECG. Finally a manual editing ensured that all R-peaks were selected and false detected peaks were deleted.

2.3. Choosing HRV-method

HRV can be analyzed using several mathematical approaches [4]. Frequency analysis of a time-period of consecutive R–R peaks is one of the most used methods. However, one of the drawbacks of this method is that a minimum of 1–2 min of ECG-data is required for recommended analysis of the parasympathetic tonus using the high frequencies of 0.15–0.4 Hz. For further analysis of the sympathetic tonus, an even longer period, of minimum of 4–5 min of ECG-data is recommended for standardized HRV-analysis of the low frequencies of 0.04–0.15 Hz [4]. In search of the instantaneous maximal sympathetic tonus and minimal parasympathetic tonus during seizures, we therefore used the Lorentz plot method [11]. The method has been documented to measure changes in both sympathetic and parasympathetic tonus using only 100 consecutive R–R intervals [11]. As a vast majority of both epileptic seizures and PNES seizures have been documented to be accompanied by tachycardia [1,6,9], a Lorenz plot HRV-analysis during seizures will only require about one minute for an estimate of both the sympathetic and parasympathetic tonus. The exact timing of the maximal peak of the sympathetic tonus during epileptic seizure have been shown to vary greatly from seizure to seizure and patient to patient [6]. To find the peak of the sympathetic tonus we therefore used a moving window model that analyze the previous 100 R–R intervals for each new R-peak during the immediate pre-ical, ictal and immediate post ictal period of each seizure.

2.4. 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) [11] (see Fig. 1). An estimation of the sympathetic and parasympathetic

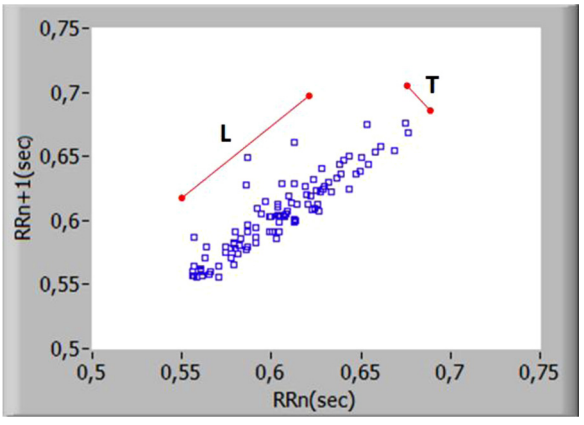

Fig. 1. Lorenz plot: Example from non-seizure rest with 100 R–R intervals (epilepsy patient 7). The transverse axis (T) reflects beat-to-beat variation ($T = 4 \times SD1$), while the longitudinal axis (L) reflects the overall fluctuations ($L = 4 \times SD2$).