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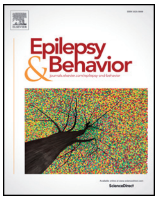

# Autonomic nervous system functioning associated with psychogenic nonepileptic seizures: Analysis of heart rate variability

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ABSTRACT

*Objective:* Psychogenic nonepileptic seizures (PNESs) resemble epileptic seizures but originate from psychogenic rather than organic causes. Patients with PNESs are often unable or unwilling to reflect on underlying emotions. To gain more insight into the internal states of patients during PNES episodes, this study explored the time course of heart rate variability (HRV) measures, which provide information about autonomic nervous system functioning and arousal.

*Methods:* Heart rate variability measures were extracted from double-lead electrocardiography data collected during 1–7 days of video-electroencephalography monitoring of 20 patients with PNESs, in whom a total number of 118 PNESs was recorded. Heart rate (HR) and HRV measures in time and frequency domains (standard deviation of average beat-to-beat intervals (SDANN), root mean square of successive differences (RMSSD), high-frequency (HF) power, low-frequency (LF) power, and very low-frequency (VLF) power) were averaged over consecutive five-minute intervals. Additionally, quantitative analyses of Poincaré plot parameters (SD1, SD2, and SD1/SD2 ratio) were performed.

*Results:* In the five-minute interval before PNES, HR significantly ($p < 0.05$) increased ($d = 2.5$), whereas SDANN ($d = -0.03$) and VLF power ($d = -0.05$) significantly decreased. During PNES, significant increases in HF power ($d = 0.0006$), SD1 ($d = 0.031$), and SD2 ($d = 0.016$) were observed. In the five-minute interval immediately following PNES, SDANN ($d = 0.046$) and VLF power ($d = 0.073$) significantly increased, and HR ($d = -5.1$) and SD1/SD2 ratio ($d = -0.14$) decreased, compared to the interval preceding PNES.

*Conclusion:* The results suggest that PNES episodes are preceded by increased sympathetic functioning, which is followed by an increase in parasympathetic functioning during and after PNES. Future research needs to identify the exact nature of the increased arousal that precedes PNES.

## 1. Introduction

Psychogenic nonepileptic seizures (PNESs) are episodes of movement, behavior, or sensations that resemble epileptic seizures but are not accompanied by epileptiform brain activity on electroencephalogram (EEG). The underlying cause is assumed to be of psychogenic origin. The current diagnostic manuals (DSM-IV-TR, ICD-10) classify PNESs as dissociative or conversion symptoms. Hence, PNESs are considered as involuntary somatic manifestations of emotional distress [1,2]. However, patients often do not report the feelings (e.g., stress, anxiety) that are associated with an episode as well as possible stressors. Nevertheless, some patients describe a “warning” uncomfortable feeling that can last up to hours, followed by a relief from this feeling by the PNES [3].

Investigation of more objective physiological parameters that reflect arousal, which possibly reflects (negative) emotional well-being, could elucidate the circumstances of the episodes, which would facilitate diagnosis and treatment in patients with PNESs [4]. Specifically, measures of heart rate variability (HRV) have often been applied in behavioral science and medicine. Changes in HRV measures reflect changes in (co)activation of the sympathetic and parasympathetic branches of the autonomic nervous system [5]. Stress and anxiety – which elicit

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the sympathetic branch of the autonomic nervous system to initiate a fight or flight response – counteract the parasympathetic (vagal) branch that is considered important for reacting appropriately to external stressors [6,7]. Patients with PNESs are expected to demonstrate decreased vagal functioning, as is found in patients with posttraumatic stress disorder [8], major depression [9], panic disorder [10], and schizophrenia [11]. Indeed, between-group analyses of patients with PNESs and healthy controls indicate a reduced resting vagal tone in patients with PNESs [12–14]. In addition, vagal tone is demonstrated to decrease during PNES episodes compared to rest [14].

Ictal changes in HRV have been described in some detail by Ponnusamy et al. [14] who compared two 3-minute ECG samples, one ictal ECG interval and one interictal ECG interval that was chosen regardless of its occurrence in time in relation to the seizure, in order to elucidate differences in autonomic functioning between patients with epilepsy and patients with PNESs. They identified decreased vagal tone during PNES episodes and an even larger decrease of vagal tone during epileptic seizures. However, based on their study design, no conclusions can be drawn about the periictal pattern of autonomic nervous system functioning that accompanies a PNES episode. Examination over consecutive recording periods may provide more information about gradual changes in measures of HRV. The current study used a within-subject design to investigate the relationship between gradual changes in HRV and the occurrence of PNESs.

## 2. Materials and methods

### 2.1. Study population

The study population consisted of twenty patients (2 M/18 F) with a confirmed diagnosis of PNESs. All patients who had been previously monitored with video-EEG for 1–7 consecutive days between July 2010 and February 2012 in the Reference Centre for Refractory Epilepsy of Ghent University Hospital in Belgium for differential diagnosis of PNESs and epilepsy were considered for inclusion. The diagnosis of PNESs was based on the analysis of at least two episodes captured on video-EEG by two epileptologists with extensive experience in this field (KEV and PAB, >10 years experience). Patients with dual pathology (epilepsy and PNESs) were also included when epileptic seizures were controlled and when the PNESs were confirmed by video-EEG monitoring. Exclusion criteria were uncertainty about the diagnosis of PNESs and comorbid psychiatric disorders (e.g., mood and anxiety disorders, schizophrenia and psychosis, and substance-related disorders). The investigation received ethical approval from the Medical Ethical Committee of Ghent University.

### 2.2. Electrocardiogram recordings

The ECG was recorded via precordial electrode positions V1–V4 throughout the video-EEG monitoring period (1–7 days) with a two-lead channel of the Micromed EEG system (Micromed S.p.A., Mogliano Veneto, Treviso, Italy). The incidence of artifacts was limited by asking the patients to stay in supine position in bed or on a chair during the day and lying down in bed during the night. The start and end of a PNES were defined by the associated motor symptoms (verified by the video recordings), which were often accompanied by unresponsiveness.

### 2.3. Heart rate variability analysis

Heart rate variability measures were derived according to the recommendations of the task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [5]. Electrocardiogram data were exported from the Micromed reporting system and imported in Matlab (Mathworks Inc., Natick, MA, USA). Custom-built Matlab scripts were used to subsequently carry out R-peak detection, model-based validation, and – if necessary – correction of the list of subsequent RR intervals (tachogram) and HRV parameter calculation over consecutive five-minute intervals.

Two time-domain measures of HRV were calculated: SDANN (standard deviation of the average beat-to-beat intervals) and RMSSD (square root of the mean squared difference of successive beat-to-beat intervals). Standard deviation of average beat-to-beat intervals, in general, reflects the overall cyclic nature of HRV (the more sinusoidal the tachogram is, the higher the SDANN) and is considered to be a measure of overall variability. The square root of the mean squared difference of successive beat-to-beat intervals is considered to be a measure for vagal control of heart rate but also includes respiratory sinus arrhythmia, i.e., the local, intrathoracic effect in HR fluctuations caused by respiratory pressure change during breathing.

Frequency-domain measures of HRV were calculated, using fast Fourier transformation to derive the spectral distribution. Indices included high-frequency (HF) power (.15–.40 Hz), low-frequency (LF) power (.04–.15 Hz), and very low-frequency (VLF) power (3–30 mHz). Efferent vagal activity is a major contributor to the HF component, as has been consistently demonstrated by clinical and experimental observations [15–17]. Consequently, HF power can be seen as a reliable index of parasympathetic nervous system activity. The interpretation of the LF component is more controversial; some studies suggest LF power to be a marker of sympathetic modulation [17–20], while others conclude LF power to be a parameter that includes both sympathetic and vagal influences [15,21]. As a result, it is unclear whether the ratio of the latter two indices (LF/HF) can be regarded as a measure of sympathovagal balance or of sympathetic modulations. The physiological correlates of lower frequency components (VLF) of HRV are still unknown [5].

Quantitative analyses of Poincaré plot parameters were also performed. The Poincaré plot (Fig. 1) is a plot of RR (n) on the *x*-axis versus RR (n + 1) on the *y*-axis; it plots the duration of each RR interval against the duration of the next RR interval. The technique most commonly used to quantify a Poincaré plot is fitting an ellipse to the plot [22–25]. We obtained the standard deviation of instantaneous inter-beat interval (IBI) variability, SD1 (which measures the width of the Poincaré cloud) [25–28], the standard deviation of continuous long-term IBI variability, SD2 (which measures the length of the Poincaré cloud) [25–28], as well as the SD1/SD2 ratio. As a measure of instantaneous changes in IBI, SD1

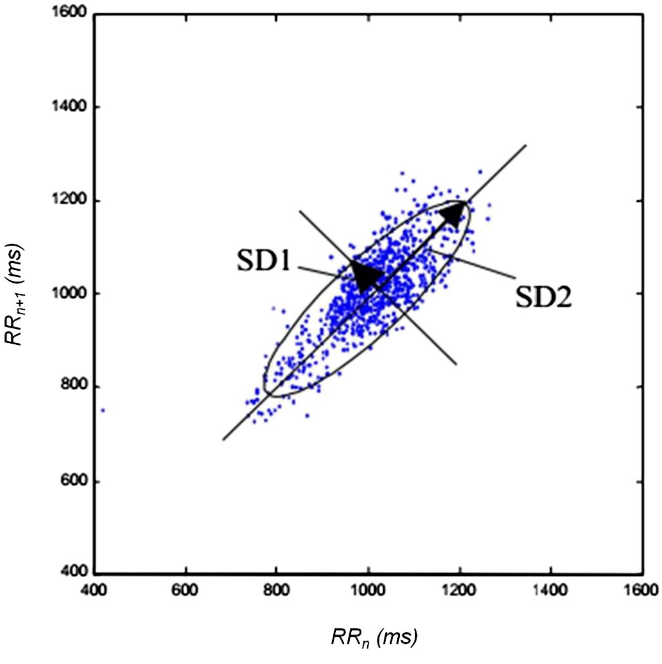

**Fig. 1.** An example Poincaré plot.