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Methodological issues in the spectral analysis of the heart rate variability: Application in patients with epilepsy

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ABSTRACT

Purpose: Spectral analysis of heart rate variability (HRV) constitutes a useful tool for the evaluation of autonomic function. However, it is difficult to compare the published data because different mathematical approaches for the calculation of the frequency bands are applied. Our aim was to compare the HRV frequency domain parameters obtained by application of 2 parametric and 2 non-parametric spectral methods in a group of patients with chronic epilepsy.
Methods: Sixty-eight patients and 69 healthy controls underwent a 5-min recording of RR signal, which was analyzed off-line in time and in frequency domains.
Results: The time domain parameters – variation RR ratio, standard deviation of normal-to-normal RR and coefficient of variation – were significantly lower in patients than in controls. In spectral analysis of the patient group deviation toward opposite directions of Low Frequency band ($p = 0.034$) and Total Power ($p = 0.013$) measures was detected depending on the method used. The results of Burg's and Yule-Walker's parametric methods fitted best to those of time domain estimates for both control and patient groups.
Conclusions: Epilepsy-related abnormalities of HRV were disclosed by time as well as by frequency domain analysis. In the present setting, the parametric methods proved to be superior to the non-parametric ones in matching time domain parameters of patients and healthy subjects and at the same time in detecting abnormalities of the frequency domain measures of patients with epilepsy.

1. Introduction

Autonomic nervous system (ANS) plays a vital role in cardiovascular system regulation. Impaired autonomic control upon heart rhythm has been disclosed by means of physiological or pharmacological approaches in various systematic, cardiac, neural and psychiatric diseases [1–4]. The growing interest in the evaluation of ANS function is largely due to the implication of autonomic dysregulation in the pathophysiology of sudden unexpected death of patients suffering from epilepsy or heart arrhythmias [5]. The study of heart rate variability (HRV) in short or long term RR signal recordings, at rest or under stress conditions and the measurements of time domain variables constitutes the every-day routine method to examine the autoregulatory effect on the cardiac rhythm. This analysis is also being incorporated in several electromyographic apparatus software programs. In our previous study [6], the RR interval variability at rest in a group of 71 patients with chronic epilepsy did not prove to be a sensitive index of ANS dysfunction because it was abnormal in only 7% of those patients. The application of dynamic tests, such as Valsalva maneuver and tilt ratio, increased the percentage of abnormality to 42.2% of the patients as compared to the matched control group of healthy individuals.

The supplementation of HRV time domain measurements by frequency domain analysis appeals to clinicians due to its simplicity of recording and its efficacy in evaluating the cardiovascular tone. The sympathetic and parasympathetic (vagus nerve) are the two distinct and opposite influences on heart rate modulation. By decomposing the frequency spectrum into four frequency bands it separates the sole contribution of the vagus nerve from that of the joint sympathovagal input to cardiac rhythm [7]. In recent literature an increasing number of articles have presented the

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results of power spectral analysis in patients with heart failure, myocardial infarction, epilepsy and Parkinson's disease as compared to healthy controls [4,8,9]. According to recent reviews, some of the markers of parasympathetic tone or balance between sympathetic and parasympathetic inputs might differ between patients with epilepsy and control groups but the findings of different studies were mixed or even contradictive [10,11]. A possible reason for these discrepancies could be the different mathematical approaches employed for the calculation of the Power Spectral Densities. Unlike time domain, the analysis of frequency domain variables requires sophisticated mathematical analyses, performed off-line, often via a custom-built PC program. Thus, methodological dissimilarities among studies pose obstacles to the direct comparison of published data. Moreover, there has been no attempt to compare the results of different mathematical models in order to identify the most suitable model that best serves the purposes of clinical studies.

We, therefore, undertook this study to measure the values of the frequency domain parameters obtained by the application of four different spectral methods to the same RR recordings. Secondary objectives were: (i) to detect possible changes of HRV power spectral measures in patients with epilepsies in comparison to a matched group of healthy individuals, (ii) to explore the possible correlation of the frequency domain to the time domain variables, as well as to clinical epileptic parameters, such as duration of epilepsy, seizure type and mono- or multiple-therapy.

2. Methods

2.1. Subjects

We herein applied the frequency domain analysis of the RR signal on data obtained from a group of 71 patients with various epileptic syndromes. This material has been previously analyzed for standard time domain parameters [6]. The patient group was matched by age and sex with a similar control group of healthy volunteers.

2.2. Experimental protocol

Standard environmental conditions and preparations of the examined individuals, patients and healthy controls, were maintained throughout the recordings. Ag/AgCl disk electrodes were used for recording of the electrocardiogram signal with the active electrode placed over the apex of the heart and the referenced one in the subclavical area. All individuals, following 15-min time for familiarization with laboratory conditions, underwent 5-min RR recording during normal breathing. The signals were then extracted from the electromyographic apparatus with a sampling frequency of 5 kHz and analyzed off-line, both in time and frequency domains. In 2 healthy controls and 3 patients the recording data were incomplete and/or contained too many artifacts and they were excluded from the present study.

For the pre-processing of the RR recordings, the electrocardiographic-lab toolbox developed by Carvalho and colleagues [12] together with a custom made program were used in Matlab environment (Matlab 7.10.0, The MathWorks, Inc., Natick, MA, USA). The detection of R peaks was done in two steps: first a region containing the R peak was identified: if the signal was scanned at a datapoint '*n*' and its value was greater than 0.15 times the maximum absolute value from this point '*n*' and ending 2 s later, this datapoint was kept as an index where possibly the R peak resides and the same procedure was repeated going forward by 200 ms; if no maximum was found, the same procedure was repeated at 10 ms. In the second step, a maximum absolute value, from this index '*n*' and for the next 70 ms of the signal, filtered to remove baseline, was calculated and the latency of the maximum gave the latency of the R peak.

The primary RR sequence from each subject was used to calculate the primary mean RR interval and the primary standard deviation of the RR interval. Subsequently, the ectopic beats, defined as RR intervals longer or shorter than the primary meanRR ± 3 primary SD [13], were detected by the program (repeated twice), and replaced with the linear interpolation of the previous and the next point value [14]. To avoid interpolation induced errors, only recordings with less than 5% duration of the recording with rhythm irregularities were approved for further analysis.

2.3. Analysis of the RR sequence signal

2.3.1. Time domain analysis

Following the ectopic beat detection and replacement procedure, the so-obtained RR sequence epochs, consisting of approximately 270 timepoints each, were used to calculate the following parameters: mean interbeat interval of normal beats (meanRR); standard deviation of normal-to-normal RR (SDNN) and the coefficient of variation (CV) defined as SDNN divided by the mean RR expressed in percent values [15]. An additional index in the time-domain analysis – ratio *V* – was calculated by the following formula:

$$\text{Ratio } V = \frac{\text{maxRR} - \text{minRR}}{\text{meanRR}},$$

where maxRR was the maximum normal RR interval value and minRR was the minimum normal RR interval value [16]. Ratio *V* is a dimensionless ratio which can be considered as a measure of the variation of the RR, expressing the range of RR values for a particular examination.

2.3.2. Frequency domain analysis by non-parametric methods

For the analysis of data in the frequency domain and the calculation of the Power Spectral Density (PSD), 2 non-parametric signal-processing methods were used [5,17] with custom programs written in Matlab (see Supplementary Data). To obtain uniformly spaced intervals, the RR sequence signal underwent a piecewise cubic interpolation using the "interp1" function of Matlab. The resulting signal with a new sampling frequency of 4 Hz (from now on called RR signal) is adequate for efficient calculations of the power spectrum [18]. The first non-parametric method employed the Fast Fourier Transform (FFT) [19]. After detrending each dataset, zero padding was applied so that the number of data points reached the next power of two, and FFT could be used. The result of the FFT is a coefficient, which is a complex number for every frequency. The squared moduli of these coefficients form the spectral power. The graph of spectral power versus frequency represents the power spectrum. PSD is calculated as the area under the curve of the power spectrum between the upper and lower limit of a particular band. In our study, the total PSD power was calculated as the area between 0 and 0.40 Hz (and defined as Total Power, TP). Based on this principle, the custom-made software calculated the respective power in certain frequency bands.

The second non-parametric method was based on Welch's periodogram. This method reduces possible noise in the estimated power spectra by splitting the dataset into 99% overlapping segments of length equal to the closest to the signal length power of two minus 1, applying the Hamming window and then computing the discrete Fourier transform. The length of the segment used formed a compromise between the time, the frequency resolution and the noise level reduction. Smaller windows would have provided better time resolution and reduced the noise by allowing