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Nonlinear heart rate dynamics: Circadian profile and influence of age and gender

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ABSTRACT

Heart rate variability (HRV) is used as a marker of autonomic modulation of heart rate. Nonlinear HRV parameters providing information about the scaling behaviour or the complexity of the cardiac system were included. In addition, the chaotic behaviour was quantified by means of the recently developed numerical noise titration technique. 24 h Holter recordings of a large healthy population ($N = 276$, 141 males, 18–71 years of age) were available. The goal was to investigate the influence of gender, age and day–night variation on these nonlinear HRV parameters. Numerical titration yielded similar information as other nonlinear HRV parameters do. However, it does not require long and cleaned data and therefore applicable on short (5 min) noisy time series. A higher nonlinear behaviour was observed during the night (NLdr; day: 50.8 ± 19.6%, night: 59.1 ± 19.5%; $P < 0.001$) while nonlinear heart rate fluctuations decline with increasing age (NLdr; Pearson correlation coefficient r between −0.260 and −0.319 dependent on gender and day or night, all $P < 0.01$). A clear circadian profile could be found for almost every parameter, showing in particular which changes occur during the transition phases of waking up and going to sleep. Our results support the involvement of the autonomic nervous system in the generation of nonlinear and complex heart rate dynamics.

1. Introduction

Cardiovascular structures and functions change with age, increasing the risk of developing cardiovascular disease [1]. Even during day and night periods, the autonomic cardiovascular modulation is different. Epidemiologic studies highlighted the existence of a circadian profile in the onset of adverse cardiovascular (such as acute myocardial infarction, sudden death and ventricular arrhythmia) and cerebrovascular (such as ischemic and hemorrhagic stroke) events, which occur most frequently in the morning hours [2,3]. Although the exact mechanisms underlying this circadian profile of adverse vascular events are still unknown, the sympathetic nervous system is believed to be primarily responsible that most cardiovascular diseases have their onset in the morning [4].

How the autonomic nervous system (ANS) exactly modulates the heart rate remains an open question. Heart rate variability (HRV) can be used to quantify several aspects of the autonomic heart rate modulation [5]. Standard time and frequency domain methods of HRV are well described by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [6], but they fail to show the dynamic properties of the fluctuations. Therefore, nonlinear methods are typically designed to assess the quality, scaling and correlation properties, rather than to assess the magnitude of variability like standard HRV methods do. However, in agreement with Lefebvre et al. [7] and Yamamoto and Hughson [8], it seems likely that the cardiovascular system follows some nonlinear dynamics which need to be explored further. Indeed, an important feature of a healthy cardiovascular system is adaptation, which can be defined as the capacity to respond to unpredictable stimuli. Consequently, a nonlinear behaviour would offer greater flexibility than a linear behaviour. The use of nonlinear techniques will probably give additional information related to the dynamical changes in cardiovascular control.

While the day–night difference as well as the influence of gender and age on the autonomic modulation of heart rate have often been studied, most studies were limited to the standard HRV parameters. Ramaekers et al. [9] already reported a significant difference between day and night standard HRV, reflecting a higher vagal modulation during the night while Beckers et al. [10] described a tendency for higher nonlinearity during night time. Schwartz et al. [11] found a decreasing autonomic modulation with advancing age, which already starts in childhood. With respect to gender, global autonomic activity was higher in men compared to women [12–14] while vagal modulation was similar in both sexes. Consequently, one speculates that the male population has an overall higher sympathetic drive, which is related to a higher susceptibility to fatal arrhythmia and the development of coronary artery disease [15]. According to our knowledge, hour-by-hour HRV analysis of

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Holter recordings was only studied by Bonnemeier et al. [16] and moreover restricted to time domain HRV parameters.

In this paper, not only linear but also a large set of nonlinear techniques are applied to quantify scaling behaviour and complexity. In particular, we focus on the recently developed numerical noise titration technique [17], which provides a highly sensitive test for deterministic chaos and a relative measure for tracking chaos of a noise-contaminated signal in short data segments, for example 5 min of data. The main goal of this study is to examine the nonlinear dynamics in autonomic heart rate control according to gender, age and day–night periods. Therefore, the study includes a large number of healthy subjects between adolescence and old age. We hypothesize that the chaotic behaviour, given by the numerical noise titration, is higher during night than by day and that it decreases with increasing age. In addition, hour-by-hour analysis is obtained for all nonlinear HRV parameters, enabling to investigate the 24-h profile more in detail instead of only day–night variations. The goal of this study is not say whether an observed cycle is due to the circadian rhythm or to the sleep/wake alternance as this requires ad hoc experiments such as sleep deprivation or forced desynchrony (e.g. 28 h days). Only these experiments would decouple their influences.

2. Methods

2.1. Study population

This study used the same dataset as in two previous studies by Ramaekers et al. [9] and Beckers et al. [10], but now with a focus on many nonlinear HRV techniques and their circadian profile. Two hundred and seventy-six healthy subjects (135 women and 141 men) were recruted from two centres of occupational medicine (Medi Leuven and IDEWE, Leuven, Belgium) and from a group of volunteers of the Christelijke Mutualiteiten (Health Insurance Institution, Leuven, Belgium). All participants were between 18 and 71 years of age, with at least 40 participants per 10 years age category. A detailed medical history was obtained from each participant. Subjects with diabetes, hypertension, cardiovascular, neurological or psychiatric diseases were excluded. Smoking behaviour, height, weight and education level were registered. All subjects gave informed consent to the protocol approved by the local Ethical Committee.

2.2. Data acquisition

Twenty-four hour ECG recordings were obtained using Holter monitoring (ELA Medical, sampling frequency 200 Hz). Only recorders with time tracking were used. Data acquisition and treatment has been fully explained in Aubert et al. [18]. Data were reviewed and edited by the technicians using standard Holter analysis procedures. All analyses were reviewed in detail by an expert cardiologist. Correct manual annotation was made and premature supraventricular and ventricular beats, missed beats and pauses were filtered, with omission of one subsequent beat and linear interpolation of the corresponding periods. Special attention was paid to ensuring that only $N-N$ beats with uniformly detected onsets were included in the initial tachogram. This way, type A errors (QRS detected prematurely when in fact a sinus conducted wave has not occurred) and B type errors (failing to detect an R wave that is present) could be largely avoided [19,20], as well as irregular sinus rhythms [21]. A 20%-filter [22] was used, meaning that every RR interval that differ more than 20% from the previous one, is replaced by an interpolated value, defined via spline interpolation over the 5 previous and 5 next intervals. Finally, a file containing the consecutive RR intervals, called tachogram, was exported for later processing. The 24-h recordings were split into day time (8–21 h) and night time (23–6 h).

2.3. Nonlinear HRV parameters

Nonlinear HRV parameters do not describe the amount of modulation as such, but are able to describe the scaling and complexity properties of the signal. Often used parameters which study the scaling of the system are 1/*f* slope, fractal dimension (FD) and detrended fluctuation analysis (DFA α_1 and α_2) while the complexity is addressed via the correlation dimension (CD) and approximate entropy (ApEn). Also a chaotic signature is calculated by means of the Lyapunov exponent (LE) and the numerical noise titration, a nonlinear data analysis that is recently developed by Poon and Barahona [17]. A short overview of these methods will be given as they have been used multiple times, except the noise titration technique which will be outlined in detail based on Barahona and Poon [23].

2.3.1. 1/f slope

The 1/*f* slope of the log(power) − log(frequency) plot was obtained from linear regression from 10^{-4} to 10^{-2} Hz [24]. The plots had an uneven density that might overweight for data in the higher-frequency range. Therefore, we used a logarithmic interpolation of the log–log plot, resulting in a balanced number of points for linear interpolation. A slope of −1 is an indication of scaling behaviour.

2.3.2. Fractal dimension

This method is based on the algorithm of Katz [25], which describes the planar extent of the time series. The higher the FD, the more irregular the signal.

2.3.3. Detrended fluctuation analysis

Detrended fluctuation analysis quantifies fractal like correlation properties of the time series and reveals short-range and long-range correlations. The root mean square fluctuation of the integrated and detrended data are measured within observation windows of various sizes and then plotted against window size on a log–log scale [26]. The scaling exponent DFA α indicates the slope of this line, which relates log(fluctuation) to log(window size). Both the short-term (4–11 beats) DFA α_1 and the long-term (>11 beats) DFA α_2 scaling exponents were calculated. The scaling exponent can be seen as a self-similarity parameter, which is characteristic of a fractal. Values of α around 1 are an indication of scaling behaviour.

2.3.4. Correlation dimension

In the presence of chaos, an attractor in phase space characterizes the dynamics of the system, and its complexity can be quantified in terms of the properties of the attractor. The correlation dimension (CD) can be considered as a measure for the number of independent variables needed to define the total system in phase space [27]. Here, the time delay for the reconstruction of the attractor was calculated for each recording separately by means of the autocorrelation function. The embedding dimension was varied between 2 and 30. When a finite value is found for the CD of a time series, correlations are present in the signal. To conclude whether these correlations are linear or nonlinear, a surrogate time series needs to be calculated from the signal and the difference between the CD of the original data and the CD of the surrogate data is defined by an *S* value. *S* values >2 indicate significant differences; *S* values <2 indicate no significant differences.

2.3.5. Approximate entropy

Entropy refers to system randomness, regularity, and predictability and allows systems to be quantified by rate of