Nonlinear Heart Rate Variability in a Healthy Population: Influence of Age

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Abstract

Heart rate variability (HRV) measurements are used as markers of autonomic modulation of heart rate. Numerical noise titration was applied to a large healthy population to examine the influence of age. Increasing age was associated with decreasing nonlinear behaviour and this age dependency was especially prominent during daytime and was also more pronounced in the female population.

1. Introduction

Heart rate variability (HRV) measurements are used as markers of autonomic modulation of heart rate [1]. 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 [2], but in the last decades, new dynamic methods of HRV quantification have been used to uncover apparent nonlinear fluctuations in heart rate. These nonlinear variations would enable the cardiovascular system to respond more quickly to changing conditions. Here the numerical noise titration technique [3] is used, 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. Other linear and nonlinear HRV measures are calculated too, giving the possibility to compare the results of this recently developed method with those of other techniques. The purpose of this study, taking into account a sufficiently large number of healthy subjects between adolescence and senescence, was to have an indication of the Noise Limit (NL) values, which are the output of the numerical noise titration technique, in normal healthy persons. So far, this method was only applied a few times and always to study relative differences between patient groups [4, 5]. In addition, the influence of age on nonlinear heart rate variability was investigated and compared to the literature where in healthy men, a decrease of nearly all standard HRV parameters with age was reported, while in woman, SD and SDANN showed no correlation at all with age [6].

2. Methods

2.1. Data acquisition

Twenty-four hour ECG recordings of 276 healthy subjects (135 women and 141 men between 18 and 74 years of age) were obtained in Leuven (Belgium) using Holter monitoring. After R peak detection and visual inspection by the operator for verifying the peak detection, a file containing the consecutive RR intervals, called tachogram, was exported for later processing. The 24-h recordings were split into daytime (8-21h) and nighttime (23-6h). A detailed medical history was obtained from each participant. More details concerning the study population, monitoring and preprocessing are described in [6].

2.2. Nonlinear HRV parameters

To assess the nonlinear HRV properties, several methods have been proposed in the past and are calculated here: 1/f slope, fractal dimension (FD), detrended fluctuation analysis (DFA), correlation dimension (CD), approximate entropy (ApEn) and Lyapunov exponent (LE). Numerical noise titration is a nonlinear data analysis technique that is a better alternative for LE, which is a measure of the exponential divergence of nearby states. LE fails to specifically distinguish chaos from noise and can not detect chaos reliably unless the data series are inordinately lengthy and virtually free of noise. However, those requirements are difficult, if not impossible, to fulfill for most empirical data. The different steps of the numerical noise titration algorithm are already well described in [7].

Modeling.
For any heartbeat RR time series y_n, $n = 1, 2, \cdots, N$, a closed-loop version of the dynamics is proposed in which the output y_n feeds back as a delayed input. The univariate

time series are analysed by using a discrete Volterra autoregressive series of degree d and memory κ as a model to calculate the predicted time series y_n^{calc}:

$$\begin{aligned} y_n^{calc} &= a_0 + a_1 y_{n-1} + a_2 y_{n-2} + \cdots + a_\kappa y_{n-\kappa} \\ &+ a_{\kappa+1} y_{n-1}^2 + a_{\kappa+2} y_{n-1} y_{n-2} + \cdots \\ &+ a_M y_{n-\kappa}^d \\ &= \sum_{m=1}^{M-1} a_m z_m(n) \end{aligned} \tag{1}$$

where M = $(\kappa + d)!/(\kappa! d!)$ is the total dimension. Thus, each model is parameterised by κ and d which correspond to the embedding dimension and the degree of the nonlinearity of the model (i.e. d = 1 for linear and $d > 1$ for nonlinear model). The coefficients a_m are recursively estimated from (1) by using the Korenberg algorithm.

Nonlinear detection (NLD).
The goodness of fit of a model (linear vs. nonlinear) is measured by the normalised residual sum of squared errors:

$$\varepsilon(\kappa, d)^2 = \frac{\sum_{n=1}^{N} (y_n^{calc}(\kappa, d) - y_n)^2}{\sum_{n=1}^{N} (y_n - \mu_y)^2} \tag{2}$$

where $\mu_y = 1/N \sum_{n=1}^{N} y_n$ and $\varepsilon(\kappa, d)^2$ represents a normalised variance of the error residuals. The optimal model $\{\kappa_{opt}, d_{opt}\}$ is the model that minimizes the Akaike information criterion:

$$C(r) = log\varepsilon(r) + r/N \tag{3}$$

where $r \in [1, M]$ is the number of polynomial terms of the truncated Volterra expansion from a certain pair (κ, d).

Numerical noise titration.
The NLD is used to measure the chaotic dynamics inherent in the RR series by means of numerical noise titration as follows:
1. Given a time series y_n, apply the NLD to detect nonlinear determinism. If linear, then there is insufficient evidence for chaos.
2. If nonlinear, it may be chaotic or non-chaotic. To discriminate these possibilities, add a small ($< 1\%$ of signal power) amount of random white noise to the data and then apply NLD again to the noise corrupted data. If linear, the noise limit (NL) of the data is zero and the signal is non-chaotic.
3. If nonlinearity is detected, increase the level of added noise and again apply NLD.
4. Repeat the above step until nonlinearity can no longer be detected when the noise is too high (low signal-to-noise ratio). The maximum noise level (i.e. NL) that can be added to the data just before nonlinearity can no longer be detected, is directly related to LE.

Decision tool.
According to this numerical titration scheme, NL > 0 indicates the presence of chaos, and the value of NL gives an estimate of relative chaotic intensity. Conversely, if NL = 0, then the time series may be non-chaotic or the chaotic component is already neutralised by the background noise. Therefore, the condition NL > 0 provides a simple sufficient test for chaos. Details of NLD and numerical noise titration are discussed in [3, 8].

2.3. Analysis

After resampling the RR interval time series to the mean heart rate (Hz), the numerical noise titration was applied using a 300-second window and sliding the window every 30 seconds. All described HRV parameters were calculated during daytime (8-21h) and nighttime (23-6h). Statistical analysis was performed with SPSS Windows version 11.5 (Scientific Packages for Social Sciences, Chicago, IL, USA). To test the association between the different nonlinear HRV parameters and age, a two-tailed Pearson correlation coefficient was calculated.

3. Results

All nonlinear indices were significantly correlated with age. Table 1 gives the r values for the different measures, seperately for day and night and for women and men. Especially during the day, the correlation with age was very clear and it was more pronounced in the female population. During nighttime, this relation disappeared in some parameters.

Table 1. Correlation between nonlinear HRV and age.

	Day		Night	
	Male	Female	Male	Female
ApEn	-0.271 **	-0.455 **	-0.236 **	-0.354 **
FD	-0.672 **	-0.699 **	-0.450 **	-0.531 **
LE	-0.273 **	-0.314 **	-0.067 ns	0.049 ns
CD	-0.313 **	-0.511 **	-0.198 *	-0.131 ns
DFAα_1	-0.144 ns	-0.296 **	0.115 ns	0.056 ns
DFAα_2	0.433 **	0.600 **	0.517 **	0.420 **
NL	-0.169 *	-0.220 *	-0.062 ns	0.037 ns
$1/f$	-0.241 **	-0.375 **	0.034 ns	-0.273 **

Abbreviations: see Methods
*P<0.05; **P<0.01; ns = non significant

Only DFAα_2 increased with increasing age, while all other described nonlinear HRV parameters were negatively

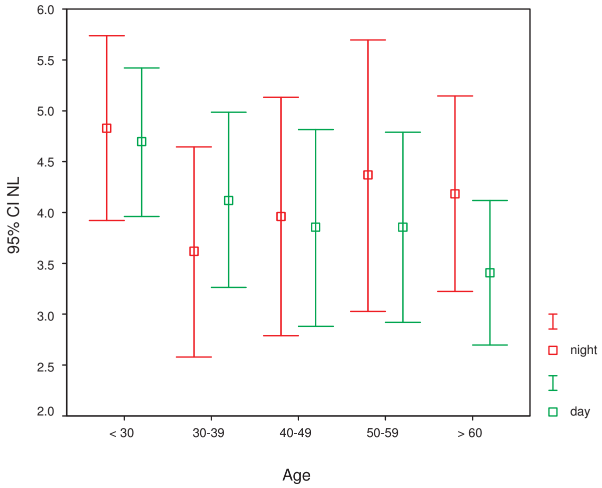

Figure 1. Mean and 95% confidence interval of NL per age category for day and night.

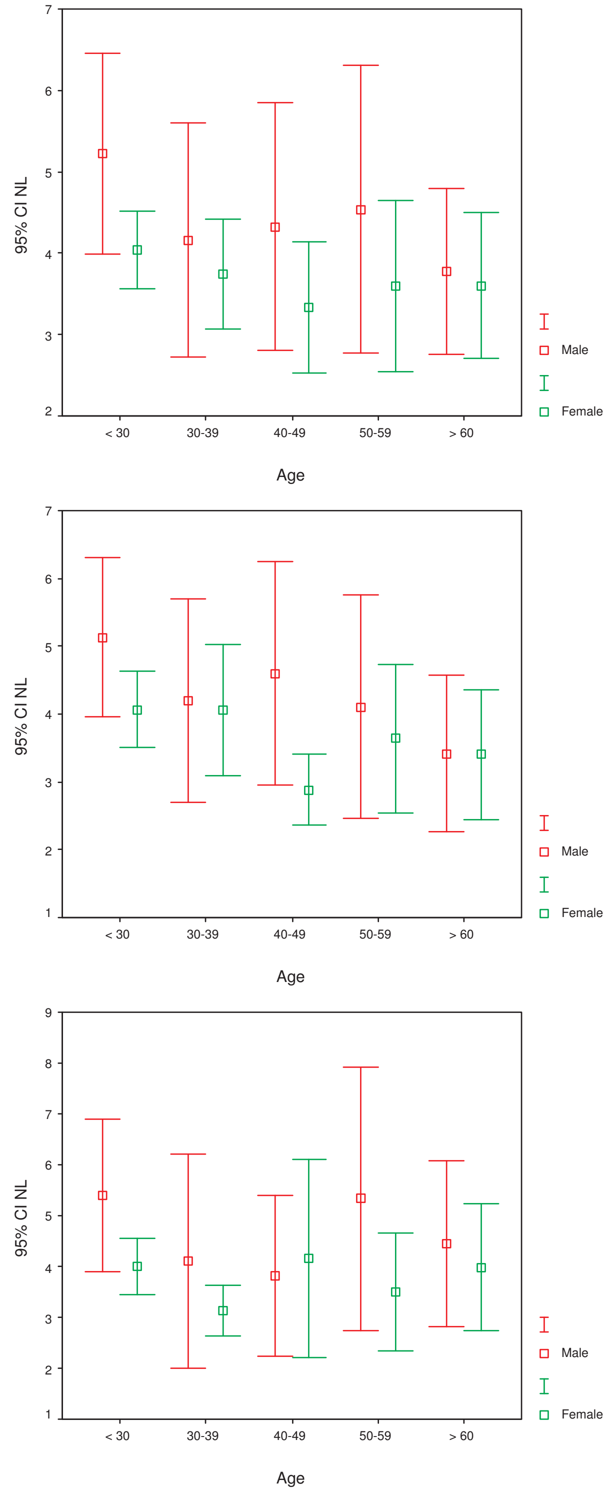

Figure 2. Mean and 95% confidence interval of NL per age category for male and female population during 24h (top), day (middle) and night (bottom).

correlated with age. The strongest relation with age could be found for FD (r between -0.45 and -0.70, P<0.001).

Being in particular interested in the output of the noise titration technique, the results per age category of 10 years are shown more in detail for day-night variation (Figure 1) and for gender difference (Figure 2). Day-night variation was age dependent in most nonlinear indices. In ApEn and DFAα_1, day-night differences were more prominent in the age classes of <50 years, whereas in LE and NL (Figure 1), it was more prominent in >50 years categories. The scatterplot (not given here) showed a decreasing NL with increasing age, which was more pronounced during day than night and in men than women. NL decreased continuously over all age categories during the day, while this pattern was not present during the night (Figure 1). This decrease during daytime is not specifically due to a certain sex, although NL is lower for women compared to men in each age class. In the category of 40-49 years, the gender difference is even strongly statistically significant during the day while there is completely no difference during the night (Figure 2). The transition behaviour from age category 40-49 to 50-59 years is also different for each sex. While NL decreases for men during daytime, but increases during nighttime, NL from women have the opposite reaction. Nevertheless, over 24h (Figure 2-top) NL increases for both sexes during that transition phase.

4. Discussion and conclusions

A strong correlation with age was detected in most nonlinear indices. Increasing age was associated with decreasing nonlinear behaviour: decrease in FD, CD, ApEn, LE, NL and a steeper $1/f$ slope. These findings are in accordance with some previous studies [9–11] and can be related to the general concept of decreasing autonomic modulation with advancing age. For those nonlinear indices, the age dependency was especially prominent during daytime and also more pronounced in the female population. Although clear evidence of a higher nonlinear behaviour of heart rate fluctuations in women was not found. An inverse association between linear HRV measures and age was already found [6,12,13]. The majority of linear HRV indices decreased with age. However linear indices in men were stronger related with age than in women [6], this study found a stronger correlation with age for nonlinear HRV measures in the female population compared to the male population as also found in [14].

A more thorough analysis per age category of 10 years showed a stabilization in the age decline of FD, ApEn and NL (Figure 2-top) at the age of $\geq$40 years. DFAα_2 continued to increase while other measures fluctuate more in each age category. This corresponds to the literature [6] in which also in linear indices the decline stabilized around the age of 40 years. The same study remarked that the gender difference narrowed and disappeared in the categories of $\geq$40 years and speculated that the protective factor may be the female hormone oestrogen. On the contrary, the NL parameter resulted in a strong difference between men and women in that age class, possibly due to the same phenomenon. However, the exact contribution is still unclear.

In summary, our study confirms earlier reports on the reduction of heart rate variability indices with increasing age, which provides again evidence for the involvement of the autonomic nervous system in the generation of these complex fluctuations. The numerical noise titration technique (NL) yields similar information as other nonlinear HRV measures do, but without need of long cleaned data. this method can be applied on short noisy time series, which can be a big advantage in clinical environment in the future.

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