# Numerical Noise Titration analysis of heart rate variability in a Healthy Population

S. Vandeput, B. Verheyden, A.E. Aubert, S. Van Huffel

***Abstract*—Heart rate variability is proposed as an indicator of cardiovascular health. Since women have a lower cardiovascular risk, one hypothesizes that there are gender differences in autonomic modulation. A large healthy population with both male and female participants was used to investigate that gender difference and to obtain a range of physiological healthy values for the nonlinear numerical noise titration technique.**

## I. Introduction

Heart Rate Variability (HRV) measurements are used as a marker of autonomic modulation of heart rate [1]. Standard time and frequency domain methods of HRV have been well described by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [2], but in recent years, 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.

Conventional spectral analysis of HRV can provide analytical features of its cyclic variation, but can not show the dynamical properties of the fluctuations. Nonlinear methods are typically designed to assess the quality, scaling and correlation properties, rather than to assess the magnitude of variability like conventional HRV methods do. Furthermore, it has been shown that the autonomic nervous system (ANS) control underlies the nonlinearity and the possible chaos of normal HRV [3]. Here the numerical noise titration technique 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.

Compared to their male counterparts, women are at less risk of coronary heart disease [4] and of serious arrhythmias [5], with women lagging behind men in the incidence of sudden death by 20 years [6]. Only some studies [7]-[9], with rather conflicting results, have focused on the influence of gender on cardiac autonomic modulation. Furthermore, these studies have several limitations, such as reporting on a small number of healthy subjects or restricting their population to a certain age category.

The purpose of this study, taking into account a sufficiently large number of healthy subjects between adolescence and old age, 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 because at the moment, this recently developed method was only applied a few times and always to distinguish different patient groups from each other [10], [11]. Furthermore, gender differences in heart rate variability were investigated. The hypothesis that HRV is higher in healthy women than in healthy men, was rejected in [12], and controlled now using a nonlinear HRV parameter.

## II. Methods

### 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 [12].

### Linear HRV

Linear HRV parameters were obtained in agreement with the standards of measurement, proposed by [2].

Mean and standard deviation (SD) of the tachogram, the standard deviation of the 5 minute average of RR intervals (SDANN), the square root of the mean of the sum of the squares of differences between consecutive RR intervals (rMSSD) and the percentage of intervals that vary more than 50 ms from the previous interval (pNN50) were calculated in the time domain.

After resampling of the tachogram at 2 Hz, power spectral density was computed by using fast Fourier transformation. In the frequency domain, low frequency power (0.04 – 0.15 Hz), high frequency power (0.16 – 0.40 Hz) and total power (0.01 – 1.00 Hz), even as the ratio of low frequency over high frequency, were calculated. In addition, the power can be expressed in absolute values or in normalized units.

### Nonlinear HRV

Numerical noise titration is a nonlinear data analysis technique that is a better alternative for the Lyapunov

exponent (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, but those requirements are difficult, mostly even impossible, to fulfill for most empirical data.

The different sections of the numerical noise titration algorithm are well described in [13].

*Modeling*.

For any heartbeat RR time series $y_n$, n = 1, 2, …, 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 $\kappa$ as a model to calculate the predicted time series $y_n^{calc}$ :

$$y_n^{calc} = a_0 + a_1 y_{n-1} + a_2 y_{n-2} + \ldots + a_\kappa y_{n-\kappa} + a_{\kappa+1} y_{n-1}^2 + a_{\kappa+2} y_{n-1} y_{n-2} + \ldots + a_M y_{n-\kappa}^d = \sum_{m=1}^{M-1} a_m z_m(n) \quad (1)$$

where $M = (\kappa + d)! / (\kappa! d!)$ is the total dimension. Thus, each model is parameterised by $\kappa$ 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:

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

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

$$C(r) = \log \varepsilon(r) + \frac{r}{N} \quad (3)$$

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 the Lyapunov exponent (LE).

*Decision tool.*

Under 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 [14], [15].

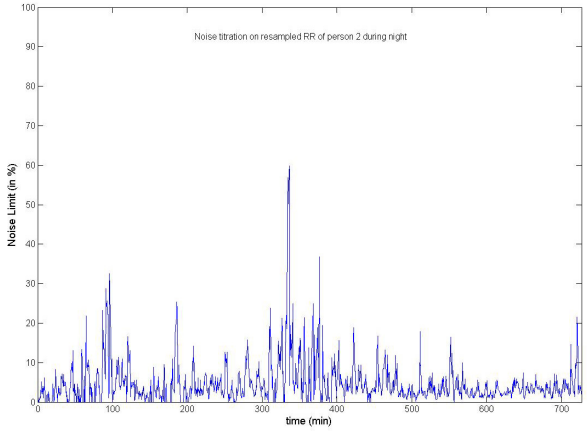


Fig. 1. Typical result of NL signal after applying the noise titration technique to a RR interval time series.

**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 standard HRV parameters and the mean Noise Limit were calculated for 24h, during daytime (8-21h) and nighttime (23-6h). Statistical analysis between men and women was done by unpaired Student's t-tests and $P < 0.05$ was considered statistically significant.

## III. Results

A typical result of applying the noise titration technique to a RR interval time series is shown in Fig.1, which also illustrates that the Noise Limit values can strongly fluctuate in time, even for the same subject under the same conditions.

The mean NL values over 24h, day and night for all 276 persons are depicted by boxplots in Fig.2. Gender differences are very small and at first sight negligible, but however, when considering the mean for each sex, one can remark a lower NL value for women in each of the three cases as can be seen in Table I. Nevertheless, that gender difference is not statistically significant as the P-values indicate.

In addition, Table II contains the mean values and standard deviations of 24h heart rate and all linear HRV parameters separately for all men and women in the study, as already described in [12]. The last column of Table II indicates for every HRV measure whether the gender difference is statistically significant or not. All HRV indices were significantly higher in men, except for pNN50 and high frequency power, both measures of the vagal modulation. Analysis of the gender difference in heart rate and HRV for the day and night separately, showed basically the same patterns, which can be seen in Table I for the NL parameter too.

TABLE I
COMPARISON OF NL VALUES (MEAN ± SD ) FOR MEN AND WOMEN

| | Day | Night | 24h |
|---|---|---|---|
| men | 4.2286 ± 3.5185 | 4.5796 ± 4.5371 | 4.3515 ± 3.4466 |
| women | 3.9358 ± 2.6123 | 3.9082 ± 3.2622 | 3.9261 ± 2.5303 |
| P | 0.4320 | 0.1580 | 0.2423 |

P-values obtained by unpaired Student's t-test to compare men and women.

## IV. Discussion

Heart rate variability is considered a parameter of cardiovascular health. Women live longer and develop cardiovascular illness at a later age than man, but evidence of higher heart rate fluctuations in the female population was not found. On the contrary, global autonomic activity, and especially the LF modulation of heart rate, was higher in men compared to women, as found previously [16]. This probably means 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 [17]. Therefore, one can hypothesize that the reduced LF power in women could protect against that disease and arrhythmia, however the exact contribution remains to be elucidated. Our results (pNN50 and HF power) also suggest that vagal modulation is similar in both sexes.

Concerning nonlinear HRV, the mean NL in healthy subjects is about 4%, which is important to know in case we want to compare with certain patient groups in future. Gender difference was not detected by the NL parameter. Reference [18] already investigated many nonlinear indices and showed only gender-related differences in approximate entropy (ApEn), short range detrended fluctuation analysis (DFA α1) and the Lyapunov exponent (LE).

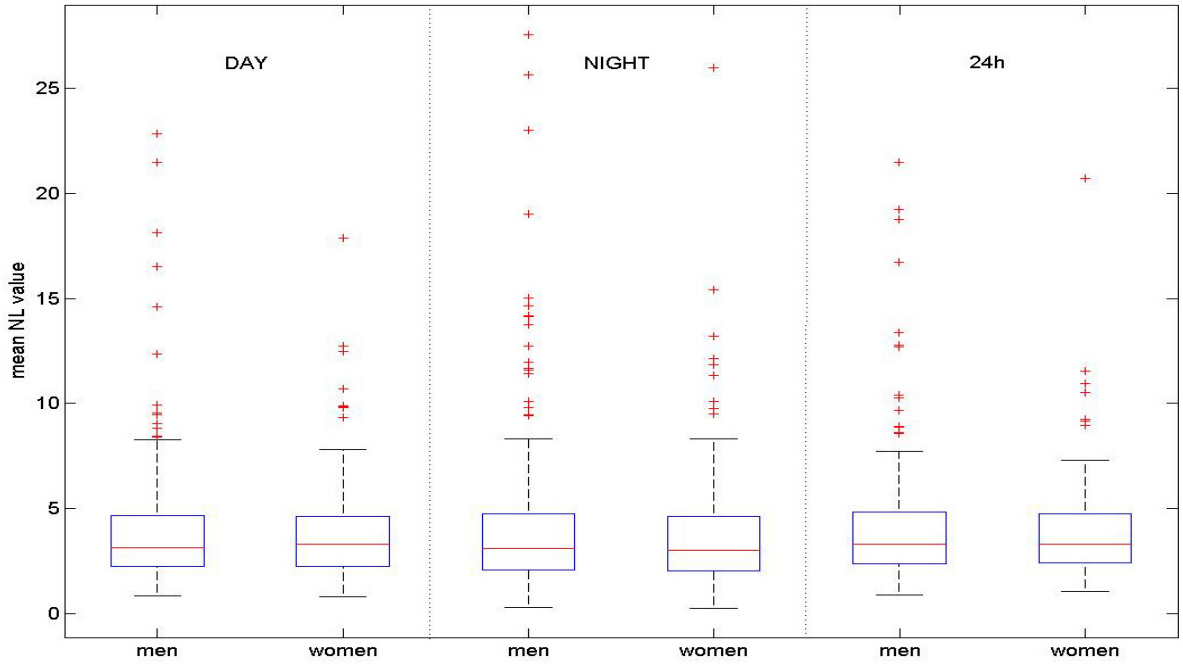


Fig. 2. Boxplot presenting the mean NL value of all 276 subjects during daytime, nighttime and over 24h, each time classified according to gender.

TABLE II
24H HEART RATE VARIABILITY INDICES (MEAN ± STANDARD DEVIATION) WITH GENDER DIFFERENCES

| | Men | Women | Gender difference |
|---|---|---|---|
| Heart rate (bpm) | 74.3 ± 8.9 | 79.1 ± 8.2 | ** |
| Time domain HRV | | | |
| SD (ms) | 157.1 ± 45.1 | 138.6 ± 29.3 | ** |
| SDANN (ms) | 141.4 ± 44.9 | 124.6 ± 29.2 | ** |
| rMSSD (ms) | 41.8 ± 22.9 | 35.4 ± 16.2 | * |
| pNN50 (%) | 11.8 ± 10.1 | 9.5 ± 7.6 | NS |
| Freq. domain HRV | | | |
| LF power ($ms^2$) | 1073 ± 701 | 704 ± 466 | ** |
| LF power (NU) | 81.7 ± 9.1 | 78.2 ± 8.4 | ** |
| HF power ($ms^2$) | 281 ± 322 | 218 ± 237 | NS |
| HF power (NU) | 18.3 ± 9.1 | 21.8 ± 8.4 | ** |
| Total power ($ms^2$) | 2690 ± 1712 | 1834 ± 1125 | ** |
| LF/HF | 5.7 ± 3.1 | 4.2 ± 1.9 | ** |
| Nonlinear HRV | | | |
| NL | 4.35 ± 3.45 | 3.92 ± 2.53 | NS |

For abbreviations, see Methods.
Significance of gender difference (after transformations to obtain normality): *P<0.05, **P<0.005, NS=non-significant.
NU=normalized units.

## V. CONCLUSION

For the first time, the numerical noise titration technique was applied to a large healthy population. In addition, gender variations were analysed. The major difference between the male and female population is in LF modulation of heart rate, while there is no evidence that nonlinear fluctuations have an impact.

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## REFERENCES

[1] S. Akselrod, D. Gordon, F. A. Ubel, D. C. Shannon, A. C. Berger, R. J. Cohen, "Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control," *Science*, 1981, vol.. 213, pp. 220-222.

[2] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, "Heart rate variability standards of measurement, physiological interpretation and clinical use," *Circulation*, 1996, vol. 93, pp. 1043-1065.

[3] A. L. Goldberger, D. R. Rigney, B. J. West, "Chaos and fractals in human physiology," *Sci Am*, 1990, vol. 262, pp. 43-49.

[4] P. W. Wilson, J. C. Evans, "Coronary artery disease prediction," *Am J Hypertens*, 1993, vol. 6, pp. 309S-313S.

[5] T. A. Manolio et al., "Cardiac arrhythmias on 24h ambulatory electrocardiography in older women and men: the cardiovascular health study," *J Am Coll Cardiol*, 1994, vol. 23, pp. 916-925.

[6] W. B. Kannel, A. Schatzkin, "Sudden death: lessons from subjects in population studies," *J Am Coll Cardiol*, 1985, vol. 5, pp. 141B-149B.

[7] S. M. Ryan, A. L. Goldberger, S. M. Pincus, J. Mietus, L. A. Lipsitz, "Gender- and age-related differences in heart rate dynamics: are women more complex men?," *J Am Coll Cardiol*, 1994, vol. 24, pp. 1700-1707.

[8] J. Molgaard, K. Hermansen, P. Bjerregaard, "Spectral components of short-term RR interval variability in healthy subjects and effects of risk factors," *Eur Heart J*, 1994, vol. 15, pp. 1174-1183.

[9] D. Liao et al, "Age, race and sex differences in autonomic cardiac function measures by spectral analysis of heart rate variability – the ARIC study," *Am J Cardiol*, 1995, vol. 76, pp. 906-912.

[10] L. Zapanta, C. S. Poon, D. P. White, C. L. Marcus, E. S. Katz, "Heart rate chaos in obstructive sleep apnea in children," *IEEE EMBC*, 2004, vol. 26, pp. 3889-3892.

[11] Z. D. Deng, C. S. Poon, N. M. Arzeno, E. S. Katz, "Heart rate variability in pediatric obstructive sleep apnea," *IEEE EMBC*, 2006, vol. 28, pp. 3565-2568.

[12] D. Ramaekers, H. Ector, A. E. Aubert, A. Rubens, F. Van de Werf, "Heart rate variability and heart rate in healthy volunteers: is the female autonomic nervous system cardioprotective?," *Eur Heart J*, 1998, vol. 19, pp. 1334-1341.

[13] S. Vandeput, F. Beckers, B. Verheyden, A. E. Aubert, S. Van Huffel, "Application of numerical noise titration during autonomic blockade," *CinC*, 2007, vol. 34, pp. 525-528.

[14] C. S. Poon, M. Barahona, "Titration of chaos with added noise," *PNAS USA*, 2001, vol. 98, pp. 7107-7112.

[15] M. Barahona, C. S. Poon , "Detection of nonlinear dynamics in short, noisy data," *Nature*, 1996, vol. 381, pp. 215-217

[16] M. J. Cowen, K. Pike, R. L. Burr, "Effects of gender and age on heart rate variability in healthy individuals and in persons after sudden cardiac arrest," *J Electrocardiol*, 1994, vol. 27 suppl., pp. 1-7.

[17] P. J. Schwartz, M. T. La Rovere, E. Vanoli, "Autonomic nervous system and sudden cardiac death. Experimental basis and clinical observations for post-myocardial infarction risk stratification," *Circulation*, 1992, vol. 85, pp. 177-191.

[18] F. Beckers, B. Verheyden, A. E. Aubert, "Aging and nonlinear heart rate control in a healthy population," *Am J Physiol Heart Circ Physiol*, 2006, vol. 290, pp. 2560-2570.