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Research Paper

COMPARISON OF HEART RATE VARIABILITY ANALYSIS METHODS IN YOUNG WOMEN DURING MENSTRUAL CYCLE

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In this paper a comparative study of linear and non-linear analysis methods, for deciphering the hidden dynamics of heart rate variability in young women during follicular and luteal phase of menstrual cycle, has been performed. In this study 25 healthy young women in the age of 18 to 25 years have been participated. The non-linear analysis methods used are: approximate entropy and largest lyapunov exponent and autoregressive method is used as a linear analysis method. The results confirmed that the heart rate variability is more in the follicular phase as compared to luteal phase of menstrual cycle. Further it has been found that the linear analysis method is not been able to differentiate between these two phases of menstrual cycle in comparison to non-linear analysis methods. Hence, approximate entropy and largest lyapunov exponent methods interpret the complexity of heart rate more significantly than an autoregressive method.

Keywords: Entropy, Follicular, Luteal, Lyapunov, Physiological, Sympathetic, Vagal

INTRODUCTION

Heart Rate Variability (HRV) has become a universal tool to study the neural control of the heart, i.e., the interaction between sympathetic and parasympathetic influences on heart rate (Malik *et al.*, 1995) in health and disease. A variety of linear, non-linear, periodical and non-periodical oscillation patterns are present in heart rate fluctuations (Aubert *et al.*, 1999a). HRV can be quantified in the time domain by the simple calculation of the mean and standard deviation of RR-intervals. In the frequency domain, spectral of HRV reveals two distinct frequency regions in the modulation of heart rate in humans. A high frequency region (0.16-0.4 Hz) which is a marker of vagal modulation, and a low frequency region (0.04-0.15Hz), which reflects predominantly sympathetic tone (Akselrod *et al.*, 1981) and baroreflex activity (Mortara *et al.*, 1997).

The menstrual cycle, characterized by sex hormone changes, is a basic physiological

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factor that continuously affects body function in women. The extent to which HRV is influenced by the menstrual cycle has been a matter of interest. For linear characteristics in HRV, self contradictory results have been reported. Most investigators (Sato *et al.*, 1995; Saeki *et al.*, 1997; Guasti *et al.*, 1999; and Yildirir *et al.*, 2002) have found increased LF components accompanied or unaccompanied by decreased HF components in HRV in the luteal phase compared with the follicular phase and concluded a predominant sympathetic activity in the luteal phase and a dominant vagal activity in the follicular phase. Moreover, Princi *et al.* (2005) found diametrically opposite results that suggested increased parasympathetic activity and decreased sympathetic activity in the luteal phase compared with the follicular phase. There is little information available in the literature about the influence of the menstrual cycle on nonlinear HRV properties (Princi *et al.*, 2005). Both time domain and frequency domain methods are based on the assumption that HRV signals are linear (Hartikainen *et al.*, 1998) and thus these methods cannot fully quantify the dynamical structure of the signal. To assess the non-linear properties, several methods have been proposed in the past: fractal dimension (Katz, 1988), Lyapunov exponents (Rosenstein *et al.*, 1993), correlation dimension (Persson *et al.*, 1996; and Bogaert *et al.*, 2001), l/f slope (Kobayashi *et al.*, 1982), approximate entropy (Pincus, 1991) and detrended fluctuation analysis (Peng *et al.*, 1996). All these methods quantify some non-linear characteristic of HRV. The non-linear methods represent potentially promising tools for heart rate variability assessment, especially in combination with the well known time and frequency domain methods.

The aim of this work was to study Heart Rate Variability (HRV) in young women during menstrual cycle with the above mentioned methods and compare nonlinear indices with spectral analysis and to compare indices in both phases of menstrual cycle.

METHODS

Subjects

Twenty five young healthy women with a mean ± SD age of 21.5 ± 3.5 years volunteered for this study. All subjects were confirmed to have no heart disease. They were non-diabetic, and non-smokers. They abstained from regular exercise, caffeine containing beverages and alcohol during the study. Their menstrual cycles were regular and ranged from 27 to 32 days (mean: 29.6 days). All subjects were familiar with the experimental processes and gave their written informed consent before participation. All female subjects were studied at each of the following phases during a single menstrual cycle: the follicular phase (days 10 ± 14) and the luteal phase (days 20 ± 24).

Data Acquisition

The ECG data of standard Lead-II for 15 minutes duration was obtained from 25 young healthy women in age group of 18-25 in our own laboratory using Biopac® MP 150 system under standardized conditions in a quiet room, at comfortable light and temperature levels. To achieve the most suitable recording conditions and better signal quality, the subjects were made to be in rest in supine position for 10 minutes prior to recording, so that the subject may stabilize to the laboratory

environment. The recorded signals were A/D converted at 500 Hz sampling frequency, 12-bit resolution and then stored and processed on an Intel PIV-processor. The recognition of QRS complexes in the ECG and the detection of R-wave were performed by means of wavelet transform.

HRV ANALYSIS

(A) Linear Analysis Method

Autoregressive Method (AR)

In parametric autoregressive model based power spectrum estimation method provide better frequency resolution than do the Fast Fourier Transform (FFT), based on nonparametric method. This is the reason we are selecting the parametric (AR model based) algorithm. The autoregressive method are based on modelling the data sequence $x(n)$ as the output of a linear system characterized by rational system function of the form given as:

$$H(z) = \frac{A(z)}{B(z)} \qquad ...(1)$$

$$= \frac{\sum_{b=0}^{q} b_k \, z^{-k}}{1 + \sum_{k=1}^{p} a_k \, z^{-k}} \qquad ...(2)$$

Corresponding difference equation is:

$$(x)^n = -\sum_{k=0}^{p} a_k \, x(n-k) \; + \; \sum_{k=0}^{q} b_k \, w \, (n-k) \qquad ...(3)$$

where $w(n)$ is the input sequence to the system and the observed data $x(n)$ represents the o/p sequence. Power spectral density of the data is:

$$r_{xx}(f) = \left|H^2(f)\right| \quad r_{ww}(f) \qquad ...(4)$$

where $r_{xx}(f)$ is the power density spectrum of the given input sequence and $H(f)$ is the frequency response of model. In the model based approach the spectrum procedure consist of two steps. Given data sequence like ECG recording $x(n)$ $0 \leq n \leq N-1$. The estimation of the parameters $\{a_k\}$ and $\{b_k\}$ of the model was done. Then from these two coefficients, the power spectrum estimate was computed. The random process $x(n)$ generated by the pole zero model is called autoregressive moving average (ARMA) (p, q) [14]. If $q = 0$ and $b_0 = 1$, the resulting system model has a system $(z) = 1/A(z)$ and its output $x(n)$ is called an autoregressive (AR) process of order p. This is the parametric AR(p) method for spectral estimate of HRV from ECG signal. The two main frequency components that represent autonomic nervous system activity are the Low Frequency (LF) components (0.04 to 0.15 Hz) and the High Frequency (HF) components (0.15 to 0.4 Hz). Frequency domain measures confirm that the LF and HF oscillatory components are relative indices of cardiac sympathetic and vagal activity respectively and HF and RMSSD indicate parasympathetic activity (Katz, 1988; and Bogaert *et al.*, 2001). We have also evaluated and analyzed the Very Low Frequency (VLF) components (0.003 to 0.04 Hz) peak, VLF power, % VLF power in the signal, LF peak, LF power, % LF power, LF power in normalized unit, HF peak, HF power, % HF power, HF power in normalized unit and the ratio LF/HF. Normalized units are obtained

$$LF(nu) = \frac{LF(ms^2) \times 100}{Total\ Power(ms^2) - VLF(ms^2)} \qquad ...(5)$$

Non-Linear Analysis Methods

Approximate Entropy (ApEn)

The ApEn is a measure of system complexity that was introduced by Pincus. It has been widely applied in cardiovascular studies. ApEn measures the degree to which the occurrence of a value depends on its predecessors in the input. High values thus imply a low predictability and regularity. It does this for a fixed no. of intervals *N*, a fixed number of predecessors and a fixed similarity tolerance *r*. Therefore there is no single ApEn value per input S_N, but a family of ApEn (S_N; *m*; *r*) values exist. The similarity tolerance r tells how much two sequences can differ while still being having a match

$$\left|HR(i+k) - HR(j+k)\right| < r \quad for\ 0 \le k \le m \qquad ...(6)$$

Consider the P_m set of all patterns of length *m* within S_m. P_m has elements $p_m(1)$, $p_m(2)$, p_m(N – *m* + 1). Then the fraction of each unique pattern in the input is defined as:

$$C_{im} = \frac{n_{im}(r)}{N - m + 1} \qquad ...(7)$$

where n_{im} is the number of patterns in P_m which are similar to $p_m(i)$. The mean of all C_{im} is denoted by C_m and measures the prevalence of repeated patterns of length *m* in S_N. The approximate entropy is then written as:

$$ApEn(S_N, m, r) = \ln\left(\frac{C_m(r)}{C_{m+1}(r)}\right) \qquad ...(8)$$

ApEn is the logarithm of the relative prevalence of repetitive patterns of length *m* compared to patterns with length *m* + 1.

Largest Lyapunov Exponent (LLE)

Lyapunov exponents tell about the sensitivity of the system to initial conditions, which is very important feature of chaotic systems. Sensitivity to initial conditions means that small changes in the state of a system will grow at an exponential rate and eventually dominate the behaviour. Lyapunov exponents are defined as the long time average exponential rates of divergence of the neighboring states. If a system has minimum one positive Lyapunov exponent, then the system is said to be chaotic. The larger the positive exponent, the more chaotic the system is (i.e., the shorter the time scale of system predictability). Lyapunov exponents will be arranged such that $\lambda_1 \ge \lambda_2 \ge \ldots \ge \lambda_n$, where λ_1 and λ_n correspond to the most rapidly expanding and contracting principal axes, respectively. Therefore, λ_n may be regarded as an estimator of the dominant chaotic behaviour of a system .The presence of a positive exponent is sufficient for diagnosing chaos and represents local instability in a particular direction. It is important to notice that for the existence of an attractor (a stable regime), the overall dynamics must be dissipative (i.e., globally stable) and the total rate of contraction must dominate the total rate of expansion. Now, consider the case of *n*-dimensional space where n is the number of state variables used to describe the system. A small *n*-dimensional hyper-sphere of initial conditions evolves into a hyper-ellipsoid as time progresses. In particular, its principal axes expand (or contract) at rates given by the Lyapunov exponents. Measurements of largest Lyapunov exponent λ_1 is calculated as a measure of the chaotic behaviour of the system using the Wolf algorithm. Consider two trajectories with nearby initial conditions on an attracting several different types. When the attractor is chaotic, the trajectories diverge, at an exponential rate characterized by the

largest Lyapunov exponent λ_1. The algorithm used is as follows:

- Compute the distance d_0 of two, very close, points in the reconstructed phase space orbit.
- Follow both points as they travel a short distance along the orbit. The distance d_1 between them is calculated.
- If d_1 becomes too large, one of the points is kept and appropriate replacement for the other point is chosen.
- The two points are now allowed to evolve again following steps 1-3.
- After these propagation steps, the largest Lyapunov exponent λ_1 is estimated as.

$$\lambda_1 = \frac{1}{t_s - t_0} \sum_{k=1}^{s} \log_2 \left(\frac{d_1(t_k)}{d_0(t_{k-1})} \right) \quad ...(9)$$

RESULTS AND DISCUSSION

In this paper, the results as shown in Table 1, are given in the form of comparative analysis between linear analysis method, i.e., autoregressive method (AR) and non-linear methods, i.e., approximate entropy (ApEn) and Largest Lyapunov Exponent (LLE) under luteal and follicular phase of menstrual cycle. The results after AR method are given in the form of normalized powers in the low frequency band (nLF) (0.04 Hz-0.15 Hz), high frequency (nHF) (0.16 Hz-0.4 Hz) and nLF/nHF ratio. These values show that nHF has a higher mean value in the follicular phase than in luteal phase while nLF was higher in luteal phase than follicular phase. These values suggest that the follicular phase was characterized by enhanced vagal activity whereas the luteal phase was characterized by enhanced sympathetic activity. The same thing is depicted using bar chart shown in Figure 1. Further for differentiating between two phases of menstrual cycle, after AR method, a *t*-test which is performed gives p value higher than 0.05. This signifies that there is not much statistically significant difference between the follicular and luteal phase of menstrual cycle. The results after applying ApEn and LLE non-linear analysis methods shows that mean values are higher in follicular phase than luteal phase indicating loss of predictability and less chaotic behaviour in luteal phase. The graphical representations of these values are shown using a bar chart in Figure 2. The *p*-value for both these non-linear indices came out to be less than 0.05 which is statistically significant for differentiating between two phases of menstrual cycle.

Table 1: Showing Linear and Non-Linear Indices of HRV

Analysis Methods		Indices	Luteal Phase (Mean ± Std. Dev.)	Follicular Phase (Mean ± Std. Dev.)	*p*-value
Linear Analysis Method	Autoregressive Method (AR)	nLF	0.472 ± 0.15	0.458 ± 0.14	0.9543
		nHF	0.528 ± 0.15	0.542 ± 0.14	0.9514
		nLF/nHF	1.098 ± 0.81	1.015 ± 0.78	0.8721
Non-Linear Analysis Methods	Approximate Entropy (ApEn)		0.313 ± 0.17	0.386 ± 0.13	0.0350
	Largest Lyapunov Exponent (LLE)		0.282 ± 0.12	0.374 ± 0.19	0.0280

Figure 1: Bar Chart Showing Normalized Power in LF Band, HF Band and LF/HF Ratio in Luteal and Follicular Phase Obtained After AR Method

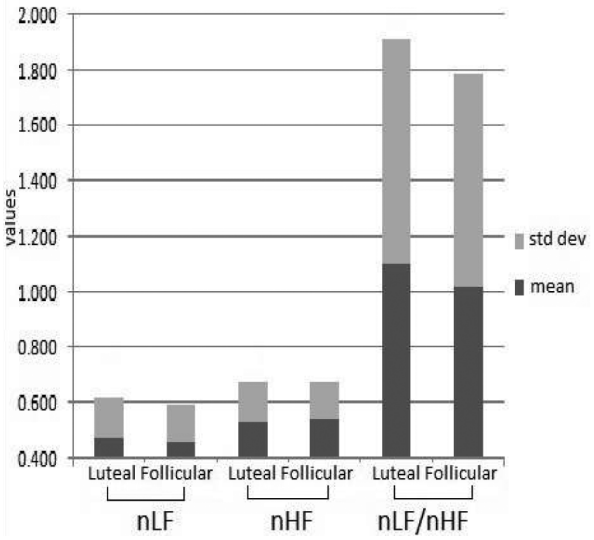
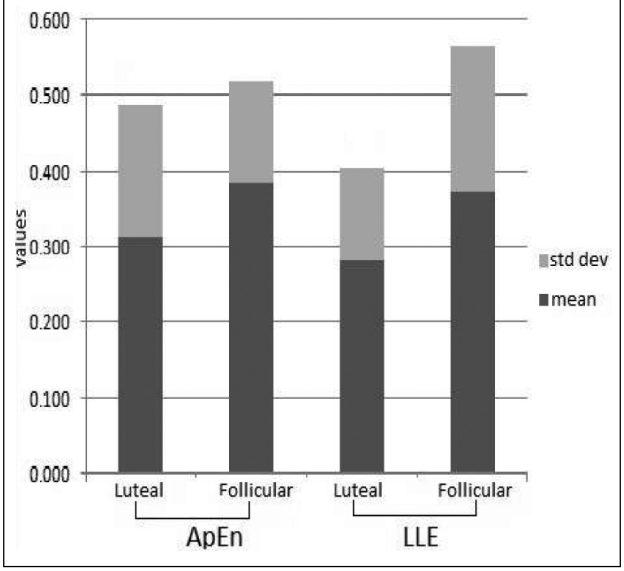


Figure 2: Bar Chart Showing Non-Linear Indices, i.e., ApEn and LLE in Luteal and Follicular Phase of Menstrual Cycle



In previous works it has been established that the linear components make up only a small part of HRV, and the nature of Heart Rate (HR) fluctuation is nonlinear (Xiaopeng *et al.*, 2009); thus the study which is performed here clearly depicts that the non-linear analysis methods more efficiently characterize the difference between luteal and follicular phase of menstrual cycle in comparison to linear analysis methods. Thus, either from the regularity or dimension of the system, results showed that more complex HR dynamics characterized the follicular phase, in comparison with the luteal phase during menstrual cycle.

CONCLUSION

It has been found that the heart rate variability in follicular phase is higher than in luteal phase of menstrual cycle. This is concluded using non-linear analysis methods of heart rate variability, i.e., approximate entropy and largest lyapunov exponent, which significantly differentiate the luteal and follicular phase in terms of heart rate variability, whereas linear analysis method, i.e., autoregressive method was unable to differentiate the luteal and follicular phase of menstrual cycle.

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