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Non-linear Analysis Approach of Maternal Heart Rate Patterns in Normal and Pre-eclamptic Pregnancies

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Identification of the pregnant woman prone to develop pre-eclampsia later during her course of the pregnancy is a clinical challenge in clinical obstetrics. A new and non-invasive approach to detect abnormalities in pre-eclamptic women that differentiate from women with uneventful pregnancies is presented here. We applied non-linear and fractal features for classifying the dynamical complexity of the heart rate (HR) patterns corresponding to seven normal subjects and eight pre-eclamptic patients. Significant differences in the estimated largest Lyapunov exponent and in the correlation dimension between normotensive women and those with pre-eclampsia were found, suggesting they may have potential as new markers for pre-eclampsia. HR patterns in healthy and pre-eclamptic pregnancies correspond to complex non-linear dynamics, which could arise from the contribution of stochastic and chaotic components. HR of pre-eclamptic patients also revealed a more regular dynamic behavior than those belonging to normal pregnancies, corroborating the general observation that diseased states may be associated with regular HR patterns.

Keywords: Pre-eclampsia; Pregnancy; Heart rate; Non-linear analysis; Correlation dimension; Lyapunov exponents

INTRODUCTION

Pre-eclampsia is the most serious medical disorder of pregnancy and constitutes a major cause of maternal and perinatal morbidity and mortality (Hauth *et al.*, 1999; Duley, 2003). Considerable controversy exits over the origin of this multi-factorial syndrome. Genetic, immunologic, environmental and vascular factors as well as oxidative stress have been invoked to play a role in its development. However, none of the theories allow prediction of which individual pregnant woman will develop pre-eclampsia and no ideal screening test is available (Bolte *et al.*, 2001). The assumption that the triggering event is linear has characterized these efforts (Eneroth-Grimfors *et al.*, 1994; Eneroth and Storck, 1998).

Complexity and complicity seem to characterize most pathophysiologic processes in pre-eclampsia, a situation suggesting that similar mechanisms must exist at the origin of the disease. The unique configuration of intervillous space and the intensity of energy transference through the fetomaternal interface offer many dysfunctional possibilities (even in clinically normal pregnancies), such as shedding and deportation of trophoblast, fragmentation of villi, escape of fetal blood and events associated with trophoblast damage, degeneration and death. Considering the convergence of multiple factors and the presence of non-linearity in some of their interactions as a plausible working hypothesis in pre-eclampsia, further exploration should adhere to the rules of this different reality (López-Llera, 1995).

Significant adaptations of the maternal cardiovascular system occur in normal pregnancy (Voss *et al.*, 2000). In pre-eclampsia, the mechanisms underlying the change from this normally adapted cardiovascular system to a vasoconstricted, hypertensive and mal-adapted system remain obscure (Cunningham and Lindheimer, 1992; Williams, 2003). One hypothesis receiving increased attention is that pre-eclampsia could arise from instabilities of the mechanisms of regulation and control of the organism, as a consequence of the oxidative stress (Hubel, 1999; Rebelo *et al.*, 1996). These instabilities provoke a change in the dynamic behavior of the pregnant, which cannot be detected in physiologic signals like the heart rate (HR), by means of traditional methods due to the non-linear character of these changes. Assuming that

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the maternal HR carries the information of the actual and the expected dynamic behavior of the pre-eclamptic patient, non-linear methods may offer an effective tool for recognizing the warning signs much earlier than at present. Previous studies have suggested other physiologic signals, such as the HR response to orthostatic stress (Ahmad *et al.*, 1996), the ratios of lactoferrin per neutrophil or per erythrocyte (Rebelo *et al.*, 1996), and the magneto-umbilicograms (MUG) (Anninos *et al.*, 1999) as possible markers for pre-eclampsia. In the case of MUG, it was reported a non-linear analysis of this signal recorded from the umbilical artery in normal and pre-eclamptic pregnancies.

In this paper, we present a computerized non-linear analysis of the heart rate patterns of a small number of subjects with or without a clinical diagnosis of pre-eclampsia. Thereto, we used conventional and non-linear methods of time series analysis like SDNN, RMSSD (Kleiger *et al.*, 1992), power spectra (Press *et al.*, 1986), attractor reconstruction and estimation of the correlation dimension (Takens, 1981; Grassberger and Procaccia, 1983) and the largest Lyapunov exponent (Eckmann and Ruelle, 1985; Wolf *et al.*, 1985; Brown, 1993). Surrogate data analysis (Theiler *et al.*, 1992) was performed to test for non-linearities. We found that non-linear methods, in particular the largest Lyapunov exponent and the correlation dimension, could reasonably distinguish between both patient groups. These findings suggest that the assessment of the HR using non-linear analysis would be useful in the prediction of future pre-eclampsia.

MATERIALS AND METHODS

Data Selection

We studied a set of consecutive maternal heart rate sequences (30–60 min duration) that were acquired at the Department of Gynecology and Obstetrics of the S João do Porto University Hospital in Portugal. This study included 15 pregnant women during the third trimester of their first pregnancy. Of these, seven were apparently normal and eight had pre-eclampsia. These women were fully informed of the details of this non-invasive study. All subjects were between 20 and 35 years old and their previous medical histories were normal.

Normal pregnancy was diagnosed on the basis of a clinical and echographical perspective. This group consisted of healthy normotensive and non-proteinuric patients throughout pregnancy, their deliveries were normal and the newborns had a normal weight. They were free from any other diseases and were not prescribed drugs affecting the cardiovascular system.

Pre-eclamptic women were nulliparous, developed hypertension, proteinuria and edema in the third trimester of their pregnancy, but were normotensive and aproteinuric on their initial visits. Hypertension was defined as two consecutive blood pressure measurements (24 h apart) of 140/90 mmHg or higher. Significant proteinuria was defined as detection of 300 mg/l protein or higher in two random samples of urine. In both groups, women who presented ecographical evidence of intrauterine growth retardation (IUGR) were excluded from this study. The comparison of age, gestational age, blood pressure and mean HR between both groups (normal and pre-eclamptic pregnant women) is shown in Table I.

Analysis of HR Sequences

The characterization of the HR sequences has been made with different approaches that can be described below. The commercial software CDA (Chaos Data Analyser) Professional Version 2.0 (Sprott and Rowlands, 1995) was applied to determine some of the dynamic magnitudes, while we developed a software for the estimation of the correlation dimension and the largest Lyapunov exponent. To test the statistical difference of each variable (non-linear measures) between normal and

TABLE I Descriptive characteristics and the results of a panel of linear and non-linear methods applied to the analysis of HR in normal and pre-eclamptic pregnancies

	Healthy pregnancy (np=7)	Pre-eclamptic pregnancy (np=8)	Significance
Maternal age (years)	26.4 ± 2.6	25 ± 2	n.s.
Gestational age (weeks)	33 ± 2.50	32.3 ± 1.85	n.s.
Blood pressure (mmHg)	106/65 ± 14/7	171/104 ± 20/6	$p < 0.05$
Heart rate, HR (beats/min)	72 ± 16	89 ± 12	n.s.
SDNN (ms)	50.3 ± 29.2	48.5 ± 26.1	n.s.
RMSSD (ms)	22.3 ± 12.4	20.5 ± 10.8	n.s.
Visual observation of HR (Fig. 1)	No appreciable differences		
Phase portraits (Fig. 1)	Attractors of complex geometric structure		
Power spectrum analysis (Fig. 1)	No appreciable differences. Some high peaks, most part of the spectra shows a broad, noise-like behavior		
Correlation dimension, D_2 (Fig. 2) For $m = 50$, $\tau = 1$	8.4–10.8	4.9–7.4	$p < 0.05$
Largest Lyapunov exponent, λ_1 (1/s) (Fig. 3) For $m = 50$, $\tau = 1$	0.10–0.14	0.07–0.10	$p < 0.05$
Surrogate data analysis:			
Correlation dimension (Fig. 4)	In favor of a non-linear component		
IFS clumpiness test (Fig. 5)	In favor of a non-linear component		

Data are represented as mean ± standard deviation; n.s: not significant; np: number of patients. Other abbreviations see text.

pre-eclamptic groups, we used unpaired Students t-tests. A p-value < 0.05 was taken to be statistically significant.

Time Domain Analysis

Time domain features are mainly those quantifying the magnitude of the HR variability (Kleiger *et al.*, 1992), such as standard deviation of consecutive normal beats (SDNN) and the square root of the mean of the summed squares of differences between adjacent NN intervals (RMSSD). We denote each of the N beat times as $t(n)$ for $n \in \{1, \ldots, N\}$. The interval between beats is indicated by $\delta(n) = t(n) - t(n-1)$. SDNN is calculated as

$$\mathrm{SDNN} = \sqrt{\frac{1}{N-2}\sum_{n=2}^{N}\left(\delta(n) - \bar{\delta}\right)^2} \tag{1}$$

where $\bar{\delta}$ is the average NN interval:

$$\bar{\delta} = \frac{1}{N-1}\sum_{n=2}^{N}\delta(n). \tag{2}$$

We calculated RMSSD as

$$\mathrm{RMSSD} = \sqrt{\frac{1}{N-2}\sum_{n=3}^{N}[(\delta(n) - \delta(n-1))]^2}. \tag{3}$$

Attractors Reconstruction

In order to estimate fractal dimensions and Lyapunov exponents, the entire phase space of a system has to be reconstructed from a single time series. Takens (1981) showed that given a discrete time series $X_n = X(t_n)$ for $n \in \{1, \ldots, N\}$, the set of points of the form

$$V_n = \left\{X_n, X_{n+\tau}, \ldots, X_{n+(m-1)\tau}\right\} \tag{4}$$

in an embedding space of dimension m, is found to be topologically equivalent to the attractor of the system generating the series.

The embedding dimension m is the number of coordinates of the reconstructed phase space, which was estimated by a false nearest neighbours' method (Abarbanel, 1997). The parameter τ, called delay, controls the aspect of the set, for small τ, the points are well correlated and, for large τ, they distribute almost uniformly. As far as HR sequences are concerned, a delay $\tau = 1$ seems to be the most reasonable choice, since longer lags may induce undue loss of spatial correlation between points (Mansier *et al.*, 1996).

Power Spectral Analysis

Spectral analysis consists in converting information in the time domain $f(t)$ into information in the frequency domain $s(\omega)$ The most widely used method for processing the studied signal is the Fast Fourier Transformation (FFT) (Press *et al.*, 1986). The set of all squared moduli of the complex numbers, resulting from FFT, for the different frequencies ω is the Power Spectral Density (PSD) function:

$$s(\omega) = \frac{1}{2\pi}\lim_{T\to\infty}\left|\int_0^T e^{i\omega t} f(t)\mathrm{d}t\right|^2. \tag{5}$$

The power spectrum of the signal is the graph of the PSD function plotted against frequency.

Correlation Dimension

One efficient method to compute attractor dimensions is by the estimation of the correlation dimension D_2, as introduced by Grassberger and Procaccia (1983). According to this method, D_2 can be estimated from an experimental time series by means of the correlation function defined as

$$C(r,m) = \lim_{n\to\infty}\frac{2}{n(n-1)}\sum_{\substack{i=1\\ i\neq j}}^{n-1}\sum_{j=1+i}^{n}\theta\left(r - \left|V_i - V_j\right|\right) \tag{6}$$

where θ is the Heaviside function [which is defined as $\theta(x) = 0$ for $x < 0$ and $\theta(x) = 1$ for $x \geq 0$], m is the embedding dimension and n is the number of vectors constructed from a time series with N samples, given by the formula $n = N - (m-1)\tau$. Intuitively, the correlation integral $C(r,m)$ is the number of all distances $|V_i - V_j|$ between each of two vectors V_i and V_j, which are smaller than a given r. For a chaotic system the correlation integral follows a power law: $C(r,m) \sim r^{D_2}$. Thus, D_2 can be estimated as

$$D_2 = \lim_{r\to 0}\left(\frac{\partial \ln C(r,m)}{\partial \ln r}\right)_m. \tag{7}$$

In the case of a chaotic signal exhibiting a strange attractor, the correlation dimension D_2 reaches a saturated level for embedding dimensions above a critical value.

Largest Lyapunov Exponent

Lyapunov exponents provide a quantitative measure of chaos by describing the divergence of nearby trajectories in phase space (Eckmann and Ruelle, 1985). Assuming that two trajectories $a_1(t)$ and $a_2(t)$ are starting with a small distance ε in the phase space, the following relation for the distance $\Delta(t)$ holds true:

$$\Delta(t) = |a_2(t) - a_1(t)| = |a_2(0) - a_1(0)|\cdot e^{\lambda t} = \varepsilon\cdot e^{\lambda t}. \tag{8}$$

Therefore, the strength of divergence in phase space depends on the magnitude of λ. In general, a system with an n-dimensional phase space has n Lyapunov exponents $\lambda_1, \lambda_2, \ldots, \lambda_n$. Each exponent gives the average rate of divergence (or convergence in the case $\lambda < 0$) along one axis in phase space. In most cases, one only needs to measure the largest Lyapunov exponent λ_1 to characterize the behavior of a system: $\lambda_1 < 0$ means that the trajectory moves towards a fixed point, $\lambda_1 = 0$ holds for periodic systems and $\lambda_1 > 0$ is an indication for chaotic or stochastic systems. An adaptation of this procedure for determining the Lyapunov exponent from experimental data sets was originally proposed by Wolf *et al.* (1985), but may fail in situations of short and/or noisy data. Several algorithms have been developed to overcome this limitation and may be superior for the application to cardiovascular and other physiological time series. In order to estimate the highest Lyapunov exponent, we used the algorithm proposed by Brown (1993).

Surrogate Data Analysis

Both stochastic and non-linear processes can affect the regularity of a time series. Therefore, one cannot discriminate between non-linear versus stochastic HR dynamics based solely on non-linear magnitudes. However, the method of surrogate data (Theiler *et al.*, 1992) can be used as an effective tool to test the null hypothesis that HR dynamics is the result of linear stochastic processes. Surrogate data are an ensemble of data sets generated using the observed data, in that major statistical properties of the original time series are preserved, but the surrogate time series is consistent with the null hypothesis enunciated above. We compared the correlation dimension (Grassberger and Procaccia, 1983) and the Iterated Function Systems (IFS) clumpiness test (Sprott and Rowlands, 1995) between the original and the surrogate (sequence- and phase-randomized) time series.

The sequence-randomized surrogate data (white noise) were created by randomizing the sequence of the original HR data values. For comparisons with the sequence-randomized surrogate, the null hypothesis is that the original data represent temporally uncorrelated noise, meaning there is no orientation in the original data. To construct the phase-randomized surrogate data set (colored noise), the original HR data were transformed by Fourier analysis, the phases were randomized and the surrogate time series was created by performing an inverse Fourier transformation using the original amplitude and the randomized phase values. Phase-randomized surrogate data have the same linear properties as the original data, but removed non-linear relations. For comparisons with the phase-randomized surrogate, the null hypothesis is that the original data represent linearly correlated noise. If both null hypotheses are rejected, it indicates non-linear chaotic or non-linear stochastic dynamics, or a combination of both.

RESULTS

Time Domain Analysis and Attractors Reconstruction

Examples of HR tracings, recorded as described above from healthy and pre-eclamptic patients, and the corresponding attractors, reconstructed according to the Takens' theorem (Takens, 1981) in a two-dimensional phase space, are represented in Figure 1. A distinction between the HR sequences and the attractors obtained from both groups using conventional methods is quite difficult, as the graphic differences between the patterns may be very subtle. Higher mean HR in pre-eclamptic patients comparing with those of normal pregnant women was observed in almost all cases (Figure 1, Table I). No significant differences were found in the conventional SDNN and RMSSD values between both patients groups. Both reconstructed attractors display no simple geometric structure, plots are geometrically unordered. However, from the visual inspection of the phase plane, one cannot assure the existence of strange attractors.

Power Spectral Analysis

The Fourier Power spectra obtained from HR data of normal and pre-eclamptic subjects are presented in Figure 1, revealing no significant differences between them when we compare different frequency domain measures such as low-frequency (0.04–0.15 Hz) and high-frequency power (0.15–0.5 Hz). A similar result has been reported in the case of maternal heart rate variability (Eneroth and Storck, 1998). Both power spectra are complex and show at least two high peaks, which appear in the low frequency range (0.04–0.15 Hz) where power accumulates. Beside these more or less periodic components, power spectra reveal a broad, noise-like behavior over a large frequency range, indicating that HR dynamics stem from multivariate sources. In some pre-eclamptic subjects, we found a little increment of the power in high frequency range, principally between 0.3–0.5 Hz, but these differences were not appreciable in all patients complicated with this disease. These characteristics of the power spectrum have been reported in HR sequences of healthy adults (Wagner and Persson, 1998). It has also been reported a markedly depression of the power spectrum of the maternal heart rate variability (Eneroth and Storck, 1998).

Whereas this method describes cyclic variations in HR, such as respiratory sinus arrhythmia, autonomic nervous system mechanisms governing beat-to-beat changes may be masked by time averaging. This is important because these mechanisms, which probably are involved in pre-eclampsia, may produce non-linearities in the temporal patterning of R–R intervals that cannot be detected with spectral-analysis techniques.

Correlation Dimension

Figure 2a shows a saturation of the correlation dimension in both cases (normal and pre-eclamptic pregnancies)

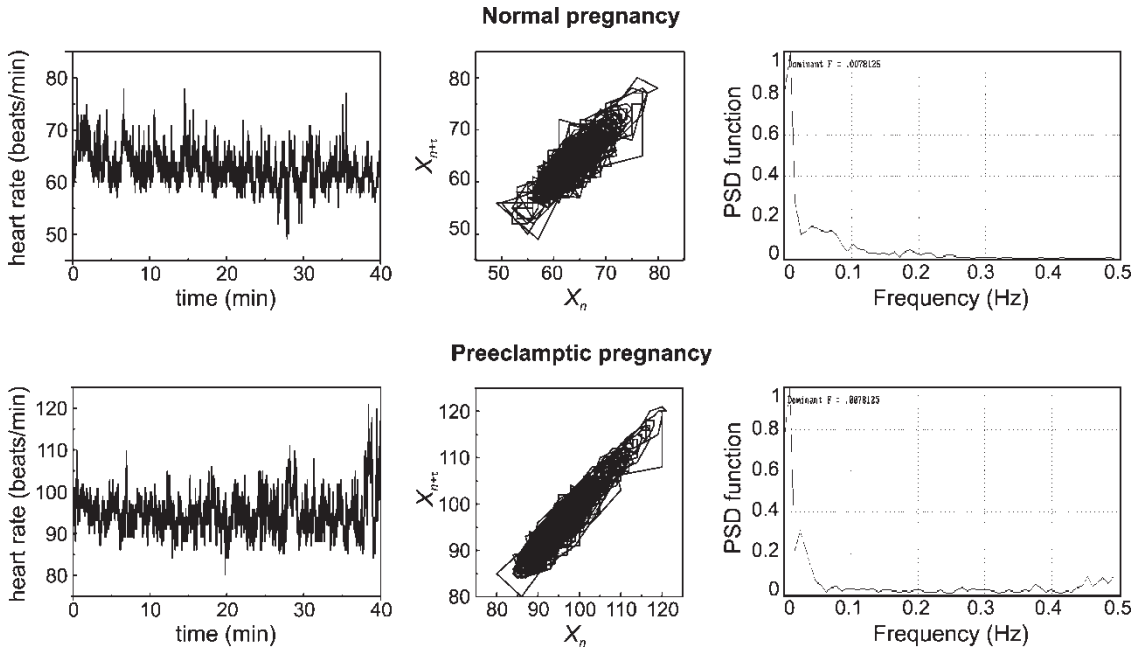

FIGURE 1 The heart rate (HR) sequences (left), reconstructed two dimensional phase-space plots (middle) and power spectra (right) of a healthy and a pre-eclamptic patient.

for embedding dimensions greater than approximately 20–25, which could be a sign of determinism if a good plateau appears in this graph. However, Figure 2a does not reveal a good saturation of the correlation dimension, and therefore for its calculation we selected an embedding dimension of 50, which was obtained applying a false nearest neighbors method (Abarbanel, 1997) instead of the classical method of saturation dimension.

In Figure 2b, we present the estimated correlation dimension values obtained from the 15 HR recordings, seven of normal (triangles) and eight of pre-eclamptic pregnancies (circles). This picture shows a tendency of estimated correlation dimension to lower values in the case of pregnancy affected by pre-eclampsia (see also Fig. 2a). Most of the pre-eclamptic pregnant women have a correlation dimension below eight, whereas the majority of the healthy ones are above this value. Except for a negative false test (pre-eclamptic patient classified as normal) and a positive false test (normal pregnant women classified as pre-eclamptic), the other data are separated by this dynamic parameter. Considering that in total only two persons gave false tests according to Figure 2b, the correlation dimension may distinguish between both groups with 86.7% of accuracy. Decreased correlation dimension in pre-eclamptic pregnancies indicates that their heart rate regulating system is less complex than that of the normal ones, which has been confirmed in other pathologies. Such a difference also reflects a decrease in the parameters which are needed in order to describe the HR pattern during pre-eclampsia.

Largest Lyapunov Exponent

Another point, illustrated in Figure 3, is the estimation of the largest Lyapunov exponent λ_1 from the reconstructed attractors. This graphic shows that the estimated largest Lyapunov exponent values could accurately distinguish between pregnant women with and without a clinical diagnosis of pre-eclampsia. Largest Lyapunov exponent in the case of healthy subjects oscillate between 0.10

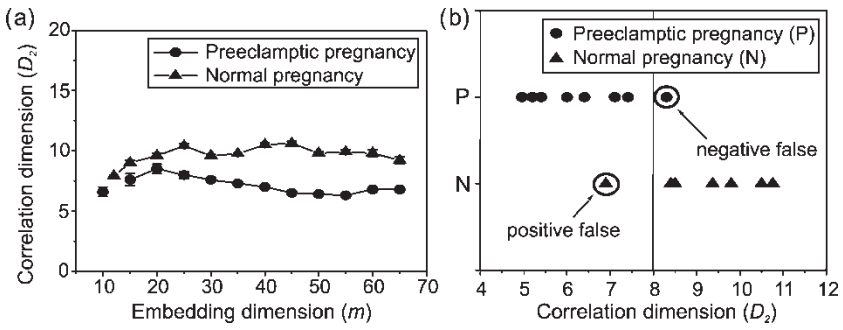

FIGURE 2 (a) Plot of the estimated correlation dimension D_2 from the original HR data versus the embedding dimension, m. (b) Estimated values of the D_2 correlation dimension obtained from the original HR recordings.

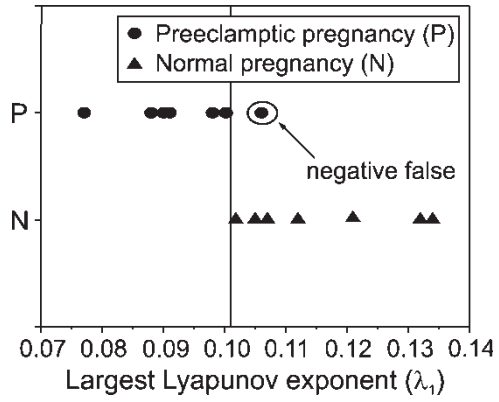

FIGURE 3 Estimated values of the largest Lyapunov exponent obtained from the original HR recordings.

and 0.14, and in pre-eclamptic patients in the range of 0.07–0.10 (Table I). Except for a negative false test (pre-eclamptic patient classified as normal), the other data are separated by this dynamic measure. Interestingly, this negative false test is stemming from the same person giving a false negative test during the estimation of the correlation dimension (Fig. 2). Thus, the largest Lyapunov exponent may discriminate between both groups with 93.3% of accuracy. In all the analyzed data, the largest Lyapunov exponent resulted to be positive, which could be evidence of chaos but also of stochastic behavior. However, the calculated values of λ_I corresponding to HR data of pre-eclamptic patients are lower than those estimated from HR of healthy pregnant women. These results suggest a more regular pattern of HR in pre-eclamptic pregnancies, which has been also obtained in other diseased states.

Surrogate Data Analysis

Surrogate data analysis of HR sequences in normal and pre-eclamptic pregnancies by comparing the correlation dimension values is shown in Figure 4, while

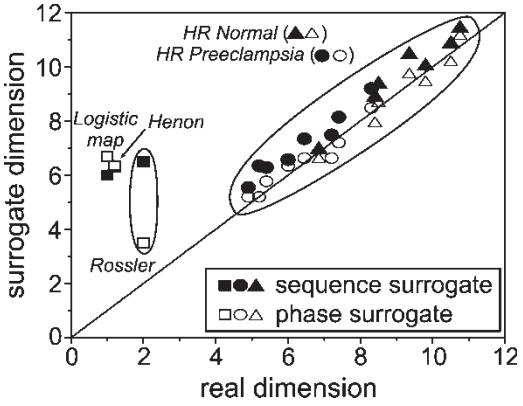

FIGURE 4 Plot of the dependence between the estimated correlation dimension of original data (real dimension) compared to that of surrogate data (surrogate dimension) corresponding to HR recording from healthy and pre-eclamptic pregnant women, Rossler, Henon and Logistic attractors (chaotic models).

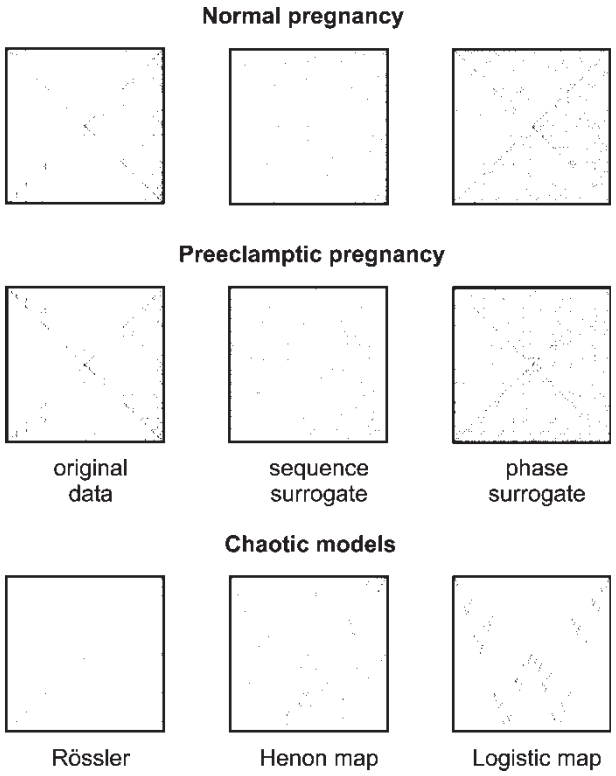

FIGURE 5 IFS clumpiness test applied to the original and surrogate HR data as well as to chaotic models. The first two rows represent the results obtained from the original HR data (left) and the corresponding sequence (middle) and phase (right) surrogate data. The first row corresponds to normal pregnancies while the second one to pre-eclamptic patient. The third row shows the behavior of distinct chaotic models: Rössler attractor (left), Hénon map (middle) and Logistic map (right).

Figure 5 illustrates the same analysis applying the IFS clumpiness test

According to Figure 4, original HR data exhibit lower dimensionality values than those from sequence surrogate and comparable, but not equal, to those from phase surrogate. Chaotic models show, however, low values in the correlation dimension (real dimension), and in all cases these values are appreciably lower than those from sequence and phase surrogate (surrogate dimension). If we enlarge the HR region of Figure 4, one can observe no appreciable differences in the dependence of the surrogate dimension upon the real dimension between pre-eclamptic and normal pregnant data. For all HR sequences, standard *t* tests, not shown here, indicated statistical differences in the mean values of the correlation dimension between original and surrogate (phase and sequence) data. Thus, both null hypotheses are rejected and therefore these results suggest the presence of non-linearity and exclude uncorrelated and linear-correlated stochastic dynamics.

Figure 5 represents the IFS clumpiness test, showing that sequence surrogate data (white noise) fill the square uniformly, while phase surrogate data (colored noise) fill also the square but make a pattern. Patterns produced by original HR data of normal subjects and pre-eclamptic patients are very similar and only partially fill the square. Chaotic models, such as Rössler attractor, Hénon map and

logistic map, produce a pattern characterized by localized clumps for the same test. Visual inspection of these squares reveals appreciable differences between original and surrogate (sequence or phase) data. HR original data produce patterns with more clumps than chaotic models. Therefore, IFS clumpiness test graphically exclude the possible presence of uncorrelated or linear-correlated stochastic dynamics as well as pure chaotic behavior.

Both surrogate data analyses suggest a non-simple non-linear dynamics displaying a structure different from the characteristic patterns generated by uncorrelated and linear stochastic models as well as by low-dimensional chaotic systems.

Table I resumes the results obtained from the assessment of the HR variability in normal and pre-eclamptic pregnancies using conventional and non-linear tools. Significant differences between both groups appear in the blood pressure, the largest Lyapunov exponent and the correlation dimension.

DISCUSSION

Mathematical modeling and computer simulation of biochemical and biological processes has become an indispensable tool for the understanding of macromolecular and cellular systems as a whole (Heinrich and Schuster, 1996; Hartwell *et al.*, 1999, Salazar and Höfer, 2003; Salazar *et al.*, 2003). Non-linear dynamics analysis based on chaos theory and fractal mathematics facilitates an accurate assessment of complex physiological signals, for example, the heart rate. These measures provide even better results than the traditional measures of time and frequency domains (Mansier *et al.*, 1996; Hoyer *et al.*, 1996; Wagner and Persson, 1998). Indeed, contradictory reports exist on the suitability of these linear indexes to describe the differences in cardiovascular variabilities between normal and pre-eclamptic pregnancies (Eneroth-Grimfors *et al.*, 1994; Voss *et al.*, 1996; Eneroth and Storck, 1998). Considering the non-linear character of the pathophysiologic processes and mechanisms involved in pre-eclampsia, we determine whether the assessment of HR sequences using non-linear parameters could discriminate between pre-eclamptic and normal pregnancies.

The principal finding of this study is that the heart rate dynamics of pre-eclamptic pregnant women are less complex and more regular than those corresponding to normal pregnancies. Non-integer correlation dimensions and positive leading Lyapunov exponents of HR sequences were found in all analyzed data. However, both parameters exhibited a significant decrease in patients affected by pre-eclampsia. Thus, these non-linear indexes may have a discriminating value in differentiating pre-eclamptic from normal pregnancies. The results of this study also indicate that classification based on conventional linear indexes like SDNN and RMSSD, spectral analysis, and visual inspection of the time series and the reconstructed attractors, may be very subtle.

The lower values of the correlation dimension and largest Lyapunov exponent obtained from the HR data of the pre-eclamptic patients point out that their heart rate regulating system is less complex and show a more regular dynamics than that of the normal subjects. This decreased system complexity in pre-eclamptic pregnancies limits the pregnant women's ability to maintain cardiovascular integrity and to adapt to the variety of cardiovascular changes during pregnancy. Our study suggests that the change from a normally adapted cardiovascular system to a vasoconstricted, hypertensive and mal-adapted system in pre-eclamptic pregnancies, could be influenced by a decrease in complexity of the heart rate dynamics.

Positive Lyapunov exponents and non-integer correlation dimensions are features of chaotic but also of stochastic dynamics. In order to characterize the underlying dynamic processes in more detail we investigated the orientation and predictability of their trajectories in the multidimensional phase space by performing the method of surrogate data, which indicated the presence of non-linear patterns. However, a clear differentiation between chaotic and non-linear correlated stochastic processes seems to be problematic in the measured HR sequences. As recent works suggest, it can be expected that the underlying physiological processes do not match with only one of these mathematical aspects (Hoyer *et al.*, 1996). Other results, exposed here, support this hypothesis: the poor saturation level observed in the curve of correlation dimension versus embedding dimension, the high values of the correlation dimension and the dimensionality values of the surrogate and original data that are not identical but comparable. On the other hand, we also found evidences of determinism. For example, the curve of correlation dimension versus embedding dimension presents a certain saturation, and in the case of a stochastic behavior, a saturation of this curve is not expected. Thus, the measured data may consist of a mixture of different deterministic and stochastic parts.

There are some limitations in our study: the small sample size (seven normal and eight pre-eclamptic pregnant women), the gestational age was not the same in all cases and the analyzed pre-eclamptic patients were affected by different grades of this disease. As pre-eclampsia is a multifactorial syndrome rather than a disease, a prospective evaluation of a larger number of subjects would strengthen the value of these preliminary observations. Since maternal heart rate dynamics may change with gestational age and different grades of pre-eclampsia, we cannot exclude the possible influence of these factors in the estimated non-linear indexes. Our calculations could be also influenced by another two factors. First, a stochastic component may be present in the heart rate signal, because all these estimates derived from non-linear dynamics assume that the time-series (HR signal) is the output of a deterministic dynamic system. Second, pre-eclamptic pregnant women were under medical treatment when heart rate recordings were obtained, which could mask the dynamic system behavior.

Pre-eclampsia is the result of a large pathophysiologic process, which imperceptibly appears many weeks before

the clinical evidence of this disease. However, the alteration of cardiovascular parameters in some women with pre-eclampsia is known to develop as early as the first trimester of pregnancy (Easterling *et al.*, 1990), suggesting a predictive value of the heart rate and other cardiovascular parameters to identify this medical disorder. We do not know the HR variability in both groups the weeks prior to development of the disease. Only if both groups of women exhibit clearly different HR patterns after non-linear analysis long before any clinical sign of pre-eclampsia had occurred, then these methods would become useful in early identification of women threatened by the disease. A prospective study is required for that.

In conclusion, several tests such as correlation dimension, highest Lyapunov exponent, and surrogate data analysis, indicate that the HR pattern of normal and pre-eclamptic pregnant women is characterized by a complex non-linear dynamics with stochastic and chaotic components. HR in pre-eclamptic pregnancy exhibits a more regular dynamics as compared with HR variability in normal pregnancy. These facts corroborate the general observation that diseased states may be associated with more regular HR patterns. Using linear methods, we were unable to differentiate between HR recordings of both clinical groups. Nevertheless, non-linear analysis, particularly the largest Lyapunov exponent and the correlation dimension, can reasonably distinguish between both types of pregnancy. Therefore, we suggest here that the assessment of HR variability using these non-linear tools may have potential as non-invasive markers for pre-eclampsia. Further research should test the prognostic value of these non-linear indexes in identifying pre-eclampsia.

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