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Characterization of systolic and diastolic pressure time series in pregnant women with preeclampsia through symbolic dynamics.

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Abstract— **Preeclampsia (PE) is one of the leading causes of maternal mortality worldwide. Although clinical strategies to prevent the early onset of PE have been proposed, the ultimate solution is to end the pregnancy. Therefore, patients' identification with major PE risk is important towards the prevention and better management of a severe manifestation of the illness. This study aims to analyze the systolic blood pressure (SBP) and diastolic blood pressure (DBP) time series through a nonlinear perspective using symbolic dynamics and to incorporate a multi-scale assessment in the first trimester of pregnancy, previous to the clinical manifestation of PE. The study group of normotensive women who developed and were diagnosed with PE included 14 pregnant women, a normotensive throughout pregnancy control group (N) consisting of 14 participants, and a group of 14 normotensive women during pregnancy without comorbidities (S) were matched with PE by age, body mass index, gestational age and comorbidities. The preliminary results of this study showed a decreased complexity of SBP, assessed by multiscale symbolic entropy in the first trimester in PE patients, in comparison with normotensive pregnant women.**

Clinical relevance— **This work shows how nonlinear analysis of systolic and diastolic blood pressure time series are useful to detect preeclampsia in the first trimester of pregnancy.**

I. INTRODUCTION

During the pregnancy, maternal autonomic cardiovascular control changes occur with the aim to optimize maternal and fetal oxygen and nutrients support. However, these cardiovascular control mechanisms can be disturbed, generating hypertensive disorders such as Preeclampsia (PE), which is a common multisystem disorder defined by the presence of high blood pressure (BP) after week 20 of pregnancy accompanied by signs such as proteinuria, severe headaches, vision affections, nausea, vomiting, thrombocytopenia, symptoms of liver or kidney damage, among others [1].

PE is one of the leading causes of maternal mortality worldwide. In Latin America and the Caribbean, 25.7% of maternal deaths are attributed to PE and in Mexico this percentage rises up to 34% [2]. Clinical manifestation of PE typically begins at the second trimester. However, an average of 21% of the patients with mild PE and 6% with severe PE may be asymptomatic [2]. Although clinical strategies to prevent early onset of PE have been proposed, the ultimate solution is to end pregnancy, which in some cases can result in adverse perinatal outcomes and maternal complications. Therefore, patients' identification with major PE risk is important towards the prevention and better management of a severe manifestation of the illness.

Blood pressure variability (BPV) has been studied to describe normal pregnancies and pregnancies with hypertensive disorders, such as PE. Increase in BPV has been reported in PE patients compared to normotensive pregnant women [3], [4]. Most of the studies regarding PE are performed when the disease is clinically manifested. However, Hermida et al. [4] showed that differences in BP between healthy and complicated pregnancies can be observed as early as in the first trimester of pregnancy and Malberg et al. [5] were able to predict PE with a predictive value of 70% several weeks before clinical manifestations, in the period between the 18th and 26th weeks of pregnancy, based on variability indexes and baroreflex parameters. Also, elevated first trimester systolic BPV was associated with PE [6].

The pathophysiologic processes in PE are a result of multiple factors and nonlinear interactions of different physiological regulations and systems could be present. Therefore, a nonlinear method could help to elucidate additional information about the behavior of systolic blood pressure (SBP) and diastolic blood pressure (DBP), considering also that biological systems operate across multiple scales of space and time. In this context, Faber et al. [3] reported a decrease of low-variability patterns in PE in comparison with healthy pregnant women using symbolic dynamics, while the joint symbolic dynamics (JSD) method was capable of demonstrating differences in the autonomic regulation between normal pregnancies and PE in the second and third trimester [7].

Thus, the aim of this study is to analyze the SBP and DBP time series by means of a nonlinear perspective using symbolic dynamics and to incorporate a multi scale assessment in the first trimester of pregnancy previous to the clinical manifestation of PE.

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II. METHODS

A. Data and Experimental Protocol

Recordings of continuous noninvasive blood pressure (CNAP) were carried out in the Maternal-Fetal Medicine Research Unit of the National Institute of Perinatology Isidro Espinosa de los Reyes (INPer). The data acquisition was performed with BIOPAC system during 5-minute in supine position in the first trimester of pregnancy, defined as the period between weeks 11 and 14 of gestation. The SBP and DBP time series were obtained as the maximum and minimum pressure value, respectively.

Exclusion criteria were comorbidities such as chronic systemic hypertension, diabetes previously diagnosed or during pregnancy, vascular disease, epilepsy, depression, anxiety, or drug addiction. Considering the International Society for the Study of Hypertension in Pregnancy (ISSHP) definition for PE [8] and the exclusion criteria, the study group of normotensive women who developed and were diagnosed with PE during second or third trimester included 14 pregnant women. However, patients in PE group had others diseases (Table I). In order to reduce heterogeneity and separate PE from comorbidities effects, a normotensive throughout pregnancy control group (N) was matched with PE by age, body mass index (BMI), gestational age (GA) and comorbidities. Also, in order to observe comorbidities effect, a normotensive women during pregnancy without comorbidities (S), control group, was paired with PE by age and GA; in S, normal BMI (BMI $\leq$ 24.9 kg/m^2) was considered. This is a retrospective study in which experimental protocol was approved by the INPer, and all participants signed an informed consent according to Helsinki guidelines.

B. Multi-scale Symbolic Entropy

For multiscale analysis, given a one-dimensional discrete time series, $x_1, x_2, x_3, ..., x_N$, a consecutive coarse-grained time series is constructed, y^τ, determined by the scale factor τ, according to (1) [9].

$$y_j^\tau = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_i,\ 1 \leq j \leq \frac{N}{\tau} \tag{1}$$

TABLE I:
Characteristics of the groups

	N (n=14)	PE (n=14)	S (n=14)
Age (Years)	32.9±4	32.6±5.5	31.7±4
BMI (Kg/m^2)	27.2±3.3	28.9±3.8	24.2±2
Hypothyroidism	7	7	0
Infertility	6	7	4
PCOS	2	2	0
PE antecedent	0	2	0
Metmorfin	5	7	0
Levothyroxine	6	7	0
Aspirin	4	6	4

Age and BMI reported as $\mu \pm \sigma$. BMI: Body Mass Index. PCOS: Polycystic Ovary Syndrome.

Each time series constructed, y^τ, is transformed into a symbol series $s_1, s_2, s_3, ..., s_N$, $s_i \in A$, with an alphabet $A = \{0, 1, 2, 3\}$ according to (2) [10].

$$s_i(x_i) = \begin{cases} 0 : \mu < x_i \leq (1+a)\mu \\ 1 : (1+a)\mu < x_i < \infty \\ 2 : (1-a)\mu < x_i \leq \mu \\ 3 : 0 < x_i \leq (1-a)\mu \end{cases} \tag{2}$$

where μ is the mean value and a is a scale parameter, $a = \{0.01, 0.03, 0.05, 0.08, 0.10\}$ were used. From s_i a new sequence is formed and is called w, composed of segments of three consecutive symbols (words), $w_i = s_i, s_{i+1}, s_{i+2}$. Each word has an overlap of two symbols with the previous word, being $w_{i+1} = s_{i+1}, s_{i+2}, s_{i+3}$.

From the distribution of words in symbolic dynamics, Shannon entropy was obtained to measure the complexity of the distribution. From words of length 3 we get Shannon entropy as follows:

$$H_k = -\sum_i p(w_i) log_2(p(w_i)), \quad p(w_i) \neq 0 \tag{3}$$

As a generalization of Shannon entropy, Renyi entropy was introduced:

$$H_k^{(q)} = (1-q)^{-1} log_2(\sum_i p(w_i)^q) \tag{4}$$

where q is a real number, different to 1. $H_k^{(q)}$ converges to Shannon entropy as q tends to 1. When $q > 1$ words of length k with large probability dominantly influence Renyi entropy. On the other hand, if $0 < q < 1$, words with small probability determine principally the value of $H_k^{(q)}$ [10]. We used $q = \{0.25, 0.50, 2, 4\}$.

Shannon entropy and Renyi entropy were implemented in a multi-scale algorithm, using scales from 1 to 5 and $a = 0.03$. Additionally, the amount of forbidden words (FW) was computed, taking into account words with a probability less than 0.1%. In order to measure variability of time series, the proportion of words that only consist of the symbols '0' and '2', WPSUM02, and the proportion of words that consist only of the symbols '1' and '3', WPSUM13, were quantified.

Another alphabet used was the max-min, where the distribution is segmented into 6 equal parts from the maximum value to the minimum value, so each subject and each experimental condition has its own range.
The levels are labeled from 0 to 5, as shown in (5) [11]:

$$s_i(x_i) = \begin{cases} 0 : min \leq x_i < min + L \\ 1 : min + L \leq x_i < min + 2L \\ 2 : min + 2L \leq x_i < min + 3L \\ 3 : min + 3L \leq x_i < min + 4L \\ 4 : min + 4L \leq x_i < min + 5L \\ 5 : min + 5L \leq x_i \leq max \end{cases} \tag{5}$$

where $L = \frac{max - min}{6}$. Then, words of length 3 are formed, creating 216 (6^3) different words which are grouped in 4 classes:

- **0V**: words without variation, 3 equal symbols.

- **1V**: words with only one variation, 2 consecutive equal symbols and a different symbol.
- **2LV**: words with 2 likely variations, words that form an upward or downward ramp.
- **2UV**: words with 2 unlikely variations, words that form a peak or valley, the 2nd symbol is greater or less than the others.

Linear indices for SBP and DBP were also calculated, such as the mean value, the standard deviation and the root mean square of successive differences (RMSSD), that is defined as the squared root of the averaged sum of squared length differences between BP values.

C. Statistical Analysis

The criterion of data normality was evaluated using the Shapiro-Wilk test with each index independently. According to the normality test results, and to obtain differences between groups, repeated measures ANOVA was used with pairwise t-tests for normal distributions or Friedman test with pairwise Wilcoxon tests for not-normal distributions, both with bonferroni adjust method for multiple comparisons. Statistically significant differences were considered with $p < 0.05$.

III. Results

The aim of both alphabets was to find out if there is a difference of symbolic dynamic parameters between the study groups. In Fig. 1 the results of multiscale symbolic Shannon entropy are shown for SBP (first row) and DBP (second row), the x axis represents scales from 1 (left) to 5 (right). In the first 3 scales, SBP values of the N group were significantly higher than in the PE group. In addition, in the first scale, Shannon entropy of S was minor than N group.

In Fig. 2 results of Renyi entropy are shown for the 3 study groups using scales from 1 (left) to 5 (right) for $q = 0.25$ (sections a and c) and $q = 4$ (sections b and d). Results of Renyi entropy for SBP with $q = 0.25$ showed significant statistical differences between N and PE groups on scales 1 and 2, where the Renyi entropy in PE is smaller than in N.

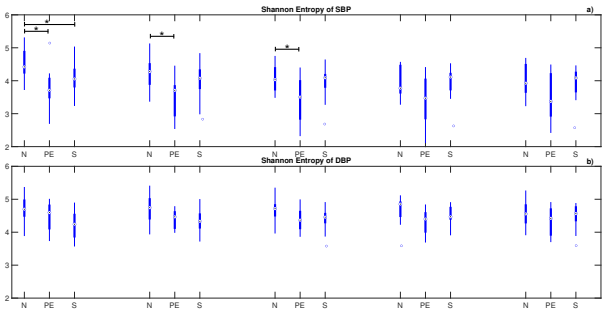

Fig. 1: Shannon entropy of systolic pressure (SBP) (a) and diastolic pressure (DBP) (b) of the 3 study groups, for scales from 1 (left) to 5 (right). $*$ indicates significant differences vs. N, with $p < 0.05$. N: Normotensive group, PE: Preeclamptic group, S: Normotensive without comorbidities group.

Besides, in the first scale, Renyi entropy of N was higher than S group. The same differences were found with $q = 4$, including the difference between N vs S, but an additional difference between N and PE groups was found in the third scale.

The results of linear analysis and both alphabets are shown in Table II. The FW index on the SBP signal showed statistical significant differences between N and PE, where N has a smaller value than PE. In the same index, differences are noted between N and S, where S has a bigger number of FW than N. In the DBP signal, N group has a higher percentage of 2LV and 2UV than the S group. We can also observe a smaller percentage of 0V for N than for S.

IV. Discussion

The results showed that multiscale symbolic entropy of SBP is able to statistically differentiate PE group from normotensive groups in the first trimester of pregnancy. To the best of our knowledge, this is the first work to analyze SBP and DBP from a multiscale point of view in PE patients. SBP of PE group showed minor Shannon and Renyi entropy values in comparison with the N and S group in the first scale, this result could suggest a decrease complexity in PE in comparison with normotensive groups, which is consistent with the result of FW being higher in PE group for SBP. Additionally, the difference between PE and N groups was present in the second and third scales, which could evidence a decrease complexity in SBP of PE patients.

Our results suggest a decrease complexity in PE patients which is contrasting with other studies, which have reported an increase BPV in PE patients in the first stages of pregnancy [4], [5], [6]. However, the current study considers pregnancy women data with a range of 11-14 weeks of gestation, few studies consider a very early stage of pregnancy for analyzing PE data. For example, Nuckols et al. [6] showed also a decreased BPV considering 9-14 weeks of gestation but they assessed the BPV by means of the oscillations in low and high frequency and, some women with PE that they included have preexisting hypertension. Additionally, Malberg et al. [5] reported an increased RMSSD value in PE patients, this index was not statistically different in our study. They also assessed symbolic dynamics indices as WPSUM02 and plvar2 which were statistically significantly reduced in PE patients suggesting an increase in DBP complexity. On the other hand, Faber et al. [3] also reported some symbolic dynamic indexes of SBP as WPSUM13 and plvar5, both indexes were lower in PE patients in comparison with control data; this result suggests less complexity in PE patients by WPSUM13, while plvar5 suggests the opposite, but the data acquisition of this study was after 30 weeks of gestation.

Regarding the comparison between N and S group, the higher 2LV and 2UV values of DBP in N group suggest a higher BP complexity. However, our results can be influenced by the added comorbidities of the pregnant women studied, although the analysis tries to avoid comorbidities effects matching by PE group by age, BMI, GA, and comorbidities, the BP time series could have a different dynamic. On the

TABLE II: Indexes of the 3 study groups, for linear and both alphabet indexes.

		Systolic Blood Pressure			Diastolic Blood Pressure		
Method	**Index**	**N**	**PE**	**S**	**N**	**PE**	**S**
Linear	**Mean value (mmHg)**	104.12 (100.92 - 116.45)	109.48 (101.21 - 115.74)	100.49 (92.58 - 108.19)	69.47 (62.82 - 72.11)	70.39 (66.59 - 73.33)	65.53 (63.22 - 72.71)
	Standard deviation (mmHg)	3.18 (2.88 - 3.97)	2.37 (1.92 - 2.84)	2.73 (2.63 - 3.30)	2.71 (2.34 - 3.30)	2.22 (2.11 - 2.67)	2.73 (2.53 - 3.01)
	RMSSD (mmHg)	1.75 (1.53 - 2.54)	1.42 (1.18 - 1.99)	1.24 (1.05 - 1.54)	2.29 (2.20 - 2.86)	1.63 (1.05 - 1.69)	1.33 (1.22 - 1.86)
4 Symbols alphabet	**FW**	25.00 (19.50 - 30.50)	37.50 (34.25 - 41.75)*	35.50 (26.75 - 38.00)*	25.00 (17.25 - 26.75)	22.50 (21.00 - 32.75)	27.00 (22.50 - 33.25)
	WPSUM02	0.24 (0.15 - 0.27)	0.28 (0.21 - 0.34)	0.21 (0.16 - 0.27)	0.17 (0.11 - 0.20)	0.23 (0.18 - 0.28)	0.17 (0.12 - 0.22)
6 Symbols alphabet	**0V (%)**	21.10 (16.32 - 29.04)	18.99 (17.40 - 38.92)	33.51 (22.74 - 41.86)	21.29 (19.35 - 34.56)	28.53 (23.37 - 40.24)	40.77 (34.38 - 50.61)*
	1V (%)	46.81 (43.88 - 48.77)	45.82 (43.49 - 47.42)	45.45 (39.85 - 47.14)	49.68 (44.09 - 50.41)	44.47 (40.61 - 49.41)	45.64 (40.63 - 47.85)
	2LV (%)	4.87 (2.96 - 6.57)	5.72 (2.88 - 6.57)	4.16 (2.69 - 6.15)	6.86 (4.52 - 9.53)	5.65 (3.59 - 9.01)	2.87 (1.45 - 4.10)*
	2UV (%)	25.07 (18.33 - 25.54)	24.78 (13.22 - 31.33)	16.71 (13.54 - 18.02)	18.34 (14.17 - 20.94)	17.63 (10.03 - 27.30)	9.72 (8.55 - 14.90)*

Values are presented as median and percentiles (25%-75%). $*$ Post hoc significant differences with N, $p < 0.05$.

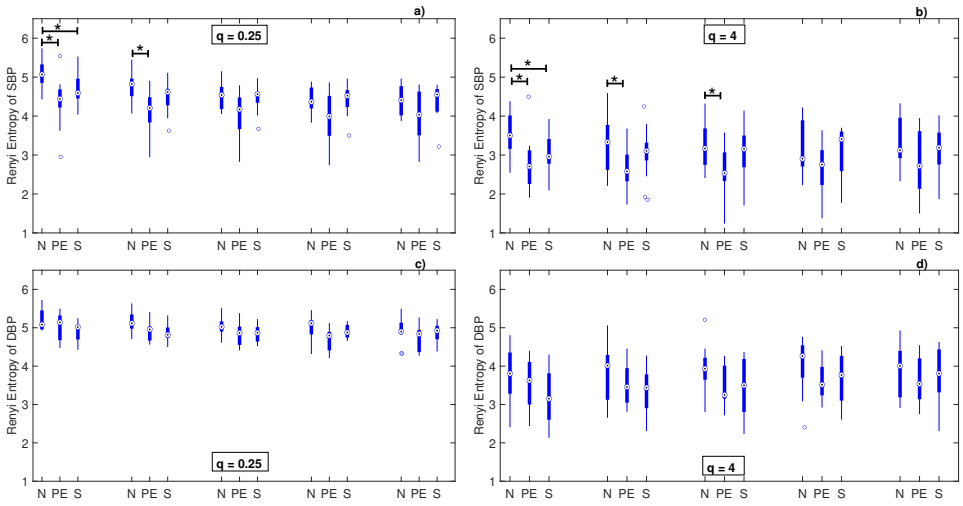

Fig. 2: Renyi entropy (RE) ($q = 0.25$ and $q = 4$) of systolic (a,b) and diastolic blood pressure (c,d) of the 3 study groups, for scales from 1 (left) to 5 (right). $*$ indicates significant differences vs. N, with $p < 0.05$. N: Normotensive group, PE: Preeclamptic group, S: Normotensive without comorbidities group.

other hand, many of the women of our study were medicated by aspirin, metformin and levothyroxine which can also affect the BP time series dynamics. In pregnant women with PCOS, the continuation of Metformin is associated with reduced rates of PE [6], while the aspirin reduces the risk of perinatal death and PE in women with historical risk factors.

V. CONCLUSIONS

The preliminary results of this study showed a decreased complexity of SBP, assessed by multiscale symbolic entropy in the first trimester in PE patients, in comparison with normotensive pregnant women. Although our results are controversial with other studies, the gestational age and additional comorbidities of pregnant women could influence the results. Therefore, these results are promising since they could allow very early detection and a better prognosis of PE, by means of a non-invasive tool such as BP signal processing, but it is important to point out the necessity of evaluating a larger population.

As a future work, it would be interesting to evaluate cardiovascular and cardiorespiratory indices through JSD, in order to get a better understanding of the first trimester changes in women that developed PE.

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