Non-Linear Analysis of Heart Rate Variability and its Application to Predict Hypotension during Spinal Anesthesia for Cesarean Delivery

Laura Canga[1,2], Augusto Navarro[3,4,5], Juan Bolea[1,2], Jose M Remartínez[3,4], Pablo Laguna[1,2], Raquel Bailón[1,2]

[1] GTC, Aragon Institute for Engineering Research (I3A), IIS Aragón, University of Zaragoza, Spain
[2] CIBER de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Spain
[3] Anesthesiology Service, University Hospital Miguel Servet, Zaragoza, Spain
[4] Aragón Health Science Institute (I+CS)
[5] Medicine School, University of Zaragoza, Spain

Abstract

A non-linear analysis of heart rate variability is carried out through two complexity measures (Correlation Dimension and Pointwise Correlation Dimension) and two regularity measures (Approximate Entropy and Sample Entropy) in order to predict hypotension episodes occurred during spinal anesthesia in cesarean delivery. These methods are applied to RR-interval series, during which woman adopts two alternative positions, one physiologically relaxed (PR) and one physiologically stressed (PS). Results show that women who developed hypotension have significantly higher (p-value $\leq$ 0.05) complexity measures at PR position, (and significantly lower values for the PS position), than those who did not developed the disease. Regarding the regularity measures, women who developed hypotension have lower values, but not arriving to significance, during PS position than those who did not developed it, whereas those values remain almost constant for PR position.

1. Introduction

Spinal anesthesia is one of the widely used methods during cesarean delivery, due to its lower maternal risk and the need of less medicalization. However, it has a disadvantage: the hypotension episodes suffered by approximately 60% of women [1]. Apart from the symptoms on the mother, anomalous pH cord values (a fetal distress indicator) have been observed. The treatment of these episodes is done through sympathomimetic drugs but, despite their high effectiveness on the maternal symptoms, the number of births in which anomalous pH cordon value has been detected does not decrease. One hypothesis that may explain this fact is that the medication administered to women who would have not developed hypotension in its absence, has adverse effects on their fetuses [2]. Therefore, it would be of great interest to identify women at risk for suffering hypotension episodes, in order to administer the medication only to those women.

Our hypothesis is that hypotension episodes may be caused by alterations in Autonomic Nervous System (ANS) regulation due to the stress induced by the impending surgery. Analysis of Heart Rate Variability (HRV) is considered as a non-invasive measure of ANS changes that has been applied traditionally from the linear perspective, in particular, with both, time and frequency methods [3]. However, in last years, the non-linear analysis of HRV has become a popular approach with promising results in prediction of hypotension during spinal anesthesia [4].

The aim of this work is to evaluate the capability of the non-linear measures correlation dimension, pointwise correlation dimension, approximate entropy and sample entropy, to predict hypotension during spinal anesthesia in a database of women referred for cesarean delivery. For comparison purposes, also de classical linear indices are considered.

2. Methods and materials

2.1. Non-linear measures

Non-linear analysis of HRV is based on chaos theory. Chaotic dynamical systems are non-linear in nature, besides being sensible to initial conditions and evolving very fast over time. Representation of these systems is done in a *d*-dimensional space known as *phase space*. Disposing of the *d* variables that define the system would be desirable, but in practice it is usual to have only one of them. Takens embedding theorem [5] proposes to reconstruct the phase space from the lagged time series available. For a time series $x(n)$ $n = 1, 2, ..., N$, where n denotes beats, the reconstructed phase space can be generated as:

$$\left\{ \begin{array}{c} \mathbf{x_1} = [x(1), x(1+\tau)\cdots x(1+(m-1)\tau)] \\ \vdots \\ \mathbf{x_i} = [x(i), x(i+\tau)\cdots x(i+(m-1)\tau)] \end{array} \right. \quad (1)$$

where $i = 1, 2, ..., N_m$ and $N_m = N - (m-1)\tau$ is the number of m-dimensional vectors reconstructed. The parameters m and τ are the embedding dimension and the time delay, respectively. A sufficient condition for the embedding dimension is given as $m \geq 2d + 1$.

All non-linear measurements described in the following are based on the Takens embedding theorem and were applied to the RR-interval series derived from the ECG as explained in Section 2.3.

2.1.1. Correlation dimension

Correlation dimension (D_2) is a measure of complexity: the more complicated the behavior of the non-linear system, the larger the correlation dimension [6]. For appropriate m and τ values, D_2 approaches to the true system dimension which, in chaotic systems, can be non integer.

In 1983, Grassberger and Procacia [7] proposed the D_2 algorithm. Firstly, the time series is normalized so that mean$(x(n)) = 0$ and max$(|x(n)|) = 1$. Then, the distance between every pair of vectors $\mathbf{x_i}$ and $\mathbf{x_j}$, constructed as in (1), is computed:

$$r_{ij} = \sqrt{\sum_{l=0}^{m-1} (x(i+l\tau) - x(j+l\tau))^2} \quad (2)$$

The correlation integral is defined as a function of the threshold distance r:

$$C_m(r) = \frac{2}{N_m(N_m-1)} \sum_{i=1}^{N_m} \sum_{j=1}^{N_m} H(r - r_{ij}) \quad (3)$$

where H(z) is the Heaviside function defined as:

$$H(z) = \left\{ \begin{array}{l} 1 \text{ si } z > 0 \\ 0 \text{ si } z \leq 0. \end{array} \right. \quad (4)$$

The relation between the correlation integral and the threshold follows a power law:

$$C_m(r) = K \cdot r^{D_2} \quad (5)$$

with K an arbitrary constant and D_2 the correlation dimension. Note that the dependency of D_2 with m has been made explicit since later will be used.

In practice, a D_2 value is calculated as the slope of ln$(C_m(r))$ against ln(r) over the linear region for different values of m. Then, the final D_2 is estimated as the value for which the slope function against m converges.

2.1.2. Pointwise correlation dimension

Pointwise correlation dimension (pD_2) can be considered the time-varying version of D_2, since a correlation integral is calculated for each vector $\mathbf{x_i}$.

$$C_m^i(r) = \frac{1}{N_m} \sum_{j=1}^{N_m} H(r - r_{ij}) \quad (6)$$

Then a correlation dimension D_2^i is estimated for each vector $\mathbf{x_i}$, generating a time series of N_m points. In this study, the histogram of the D_2^i series is calculated and the maximum is selected as the characteristic value of the series, denoted as pD_2 [4].

2.1.3. Approximate entropy

Approximate Entropy (ApEn) is a family of regularity measures that quantifies how predictable the fluctuations in a time series are. The more frequent and regular fluctuations lead to lower ApEn values. The ApEn for parameters m and r is computed as follows.

Distance between every pair of vectors $\mathbf{x_i}$ and $\mathbf{x_j}$, constructed as in (1) with no normalization and time delay τ always set to 1, is computed as:

$$d_{ij} = \max_{k=0,1,...m-1} (|x(i+k) - x(j+k)|) \quad (7)$$

For a given $\mathbf{x_i}$, a probability function is obtained:

$$C_m^i(r) = \frac{1}{N-m+1} \sum_{j=1}^{N-m+1} H(r - d_{ij}) \quad (8)$$

The average of the natural logarithm is:

$$\phi_m(r) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} \ln(C_m^i(r)) \quad (9)$$

Then, $\phi_{m+1}(r)$ is calculated and ApEn(m, r) is computed as:

$$\text{ApEn}(m, r) = \phi_m(r) - \phi_{m+1}(r) \quad (10)$$

2.1.4. Sample entropy

Richman and Moorman proposed an algorithm that outperforms ApEn in terms of consistency and bias [8]. This new regularity metric, called Sample Entropy (SampEn), is calculated as follows for input parameters m and r:

Distance between every pair of vectors $\mathbf{x_i}$ and $\mathbf{x_j}$ is computed as in (7). Then, for a given $\mathbf{x_i}$, a probability function is computed as:

$$C_m^i(r) = \frac{1}{N-m} \sum_{j=1, j\neq i}^{N-m+1} H(r - d_{ij}) \quad (11)$$

The probability that two sequences match for m points:

$$\varphi_m(r) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} C_m^i(r) \quad (12)$$

For $m+1$, $C^i_{m+1}(r)$ and $\varphi_{m+1}(r)$ are calculated. Finally, SampEn(m, r) is:

$$\text{SampEn}(m, r) = -\ln\left[\frac{\varphi_{m+1}(r)}{\varphi_m(r)}\right] \quad (13)$$

2.2. Linear measures

For comparison purposes, classical linear HRV indices were also computed using software previously developed by our group [9]. Time domain indices were calculated from the RR-interval series [3].

Frequency domain indices were obtained from the power spectral density of the modulating signal with information of the ANS, estimated from the beat occurence time series according to the integral pulse frequency modulation model as in [10], and sampled at 2 Hz. Then, absolute and normalized powers were computed in the following bands: low frequency (LF, 0.04-0.15 Hz), high frequency (HF, 0.15-0.4 Hz) and extended high frequency (HF_{EXT}, 0.15-1 Hz) band, to assure the inclusion of respiratory frequency, which in pregnant women can exceed 0.4 Hz.

2.3. Data

The ECG signal from 11 women with programed cesarean delivery was recorded with Biopac Data Acquisition MP System at 1000 Hz sample frequency, at the University Hospital Miguel Servet. Five women developed hypotension during surgery (H), while six did not (NH). See Table 1 for additional characteristics.

	H	NH
Age (years)	32.0±6.4	29.6±6.0
Gestational age (weeks)	38.5±0.5	38.8±0.9
Systolic pressure (mmHg)	106.2±12.9	105.6±18.4
Heart rate (bpm)	77.8±11.8	79.0±8.7

Table 1. Study population characteristics (mean ± sd).

Two ECG recordings are available from each woman: the first one recorded the night before the surgery, which is associated to a psychologically relaxed condition, and the second one recorded immediately before the cesarean and associated to a maximum psychologically stressed condition. During both records, women adopt two positions, lasting 7 minutes each one: lateral decubitus, a physiologically relaxed (PR) position for a pregnant woman, and supine position, during which the fetus pressure to the vena cava introduces a physiological stress (PS).

The RR-interval series were obtained using a wavelet-based ECG delineator [9]. Linear measures were computed during the central 6.5 minute-interval of lateral decubitus and supine position. Due to the sensitivity of non-linear measures to the time series length, they were computed during the central 300 point-interval. Note that the time duration of these intervals is different for each woman depending on her heart rate.

2.4. Statistical study

Firstly, the Kolmogorov-Smirnov test was applied to verify the normality of our data. Since the result was negative, the Wilcoxon signed-rank test was used to compared the median values of non-linear and linear HRV measures previously described obtained from H and NH groups. A *p-value*$\leq$0.05 was chosen as statistically significant.

3. Results

Non-linear measures D_2 and pD_2 were computed using values of the embedding dimension m ranging from 1 to 16 (appropriate values for biological signals [6]). Two time delay values were used, either a τ fixed for all the patients and equal to 1 or the optimum τ for each RR series, i.e. the value for which the autocorrelation function drops to 1/2 times its maximum [11]. Entropy measures were computed for $m = 1, 2$ and a threshold distance r equal to 0.1 times the mean of the RR-interval series standard deviation for all recordings.

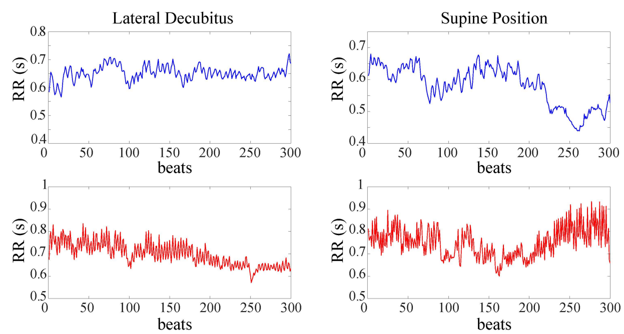

Figure 1. RR-interval series from a H subject (top) and from a NH subject (bottom), in lateral decubitus (left) and supine position (right).

A statistically significant increase in complexity measures D_2 and pD_2 with τ=1 has been appreciated for H group during the lateral decubitus position, with respect to NH group, while a statistically significant reduction has been observed during the supine position. Both changes have been detected in the recordings registered immediately before the surgery, but not in the ones registered the night before. Regarding to regularity measures ApEn and SampEn, a no statistically significant decrease has been observed for H group with respect to NH group in the supine position but not in the lateral decubitus, for m=1. As in the complexity measures, these changes occurred only during the recordings registered just before the surgery. This behavior is displayed in Fig.2.

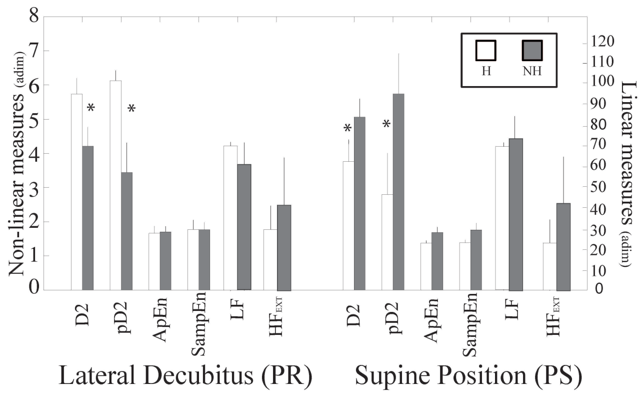

Figure 2. Median±MAD for HRV measures (* *p-value* ≤ 0.05).

Although classical linear measure results were not statistically significant, some tendencies have been observed. In the NH group, the normalized power in the LF band was lower than in the H group during the lateral decubitus and reverted in supine, while the HF_{EXT} was higher for NH during both, lateral decubitus and supine position.

4. Discussion

Complexity measures D_2 and pD_2 were significantly different between H and NH groups in both positions when computed for fixed τ=1, but not for the varying optimum τ according to [11]. The reason for this behavior remains unknown.

Just to note that this reverted behavior is coincident with the reverted LF dominancy, suggesting that D_2 and pD_2 information is related to that provided by LF, higher LF results in higher D_2 and pD_2, and the reverse. Usually LF components have higher correlation and so the results are consistent from that point of view, but in case of D_2 or pD_2 they arrive to be significant while LF does not.

Differences were also found for SampEn in both groups for m=1 and 2, while for ApEn those no significant differences were only found for m=1, supporting the idea that SampEn is a more robust measurement than ApEn.

Despite the reduced size of the database, results suggest the potentiality of non-linear analysis of HRV for the prediction of hypotension during spinal anesthesia for cesarean delivery.

5. Conclusions

In this work, a nonlinear analysis of RR-interval series has been applied to predict hypotension during cesarean delivery. Results show a reduction in both, complexity and regularity measures during the position that introduces a physiological stress (supine position) additional to the psychological stress in women who developed hypotension with respect to women who did not. During the physiologically relaxed position (lateral decubitus) an increase in complexity measures has been detected for women who developed hypotension, while regularity measures remain almost constant. Reasons for this reverted behavior remain unclear and will require further research.

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Address for correspondence:

Laura Canga
Maria de Luna 1 Ed. Ada Byron L3.07, 50015, Zaragoza (Spain)
laura.canga.garcia@gmail.com