Fetal Heart Rate Complexity Measures to Detect Hypoxia

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Abstract

Perinatal hypoxia is a severe condition that may harm fetus organs permanently or even cause dead. When the fetus brain is partially deprived from oxygen, the control of the fetal heart rate (FHR) is affected. We hypothesize that the complex physiological mechanisms of the FHR are perturbed under perinatal hypoxia. To quantify the loss in complexity we measured Sample Entropy (SampEn), Permutation Entropy (PE), and Time Irreversibility (TI). FHR traces were preprocessed to remove artifacts. A database of 32 FHR recordings were acquired with cardiotochography, 15 controls and 16 cases. Resampling methods were used to establish the statistical differences. TI was significantly different for healthy and hypoxia fetuses (-0.38 $\pm$ 0.19 vs. -0.21$\pm$0.37, p-value=0.063). Entropy indices were higher for healthy fetuses (SampEn:0.33$\pm$0.12 vs 0.28 $\pm$ 0.09, p-value=0.11; PE:0.72$\pm$0.04 vs 0.69$\pm$0.07, p-value= 0.12). We also computed temporal and spectral indices but none of them showed significant differences. Complexity measures of the FHR were different for healthy and hypoxia fetuses. These indices may help to early detect hypoxia with less invasive methods.

1. Introduction

Perinatal hypoxia is a fetus and newborn disease due to the lack of tissues oxygenation. Although it can occur in earlier gestation phases, childbirth and immediate neonatal hours are the fundamental risk periods.

Perinatal hypoxia severity spectrum conveys very mild cases (only requiring neonatal resuscitation with environmental oxygen), more serious cases needing intubation and acidosis correction with bicarbonate (reanimation types V and VI), and critical cases that can cause perinatal death or serious sequels, such as brain or adrenal hemorrhage, necrotizing enterocolitis, delayed neurological development, mental handicap, seizures (West syndrome) or cerebral palsy [1]. Diagnosis is performed at the birth time by evaluating the cardio-respiratory depression and the muscle tone. The severity of the hypoxia is commonly quantified using the Apgar Score [2], with a score lower than 7 at five minutes after delivery being considered as pathological, which is usually confirmed with gas analysis of the umbilical cord, low pH values evidence metabolic acidosis. Typical values considered for diagnosis are pH $\leq$ 7.05, wich are considered pathological in terms of risk of perinatal hypoxia.

Continuous electronic fetal monitoring, also known as Cardiotocography (CTG), was developed around 1960 [3] and consists of the simultaneous evaluation of the fetal heart rate (FHR) and the uterine activity. After CTG generalization, two relevant signs of suspicious fetal hypoxia were recognized, namely, the late decelerations of the FHR in relation to uterine contractions, and the FHR variability decrease [4, 5]. Several nonlinear indices has been used to estimate the loss of complexity in FHR under the assumption that less complex signals indicate pathological situations [6–8].

We aimed to assess the change in complexity, due to hypoxia, of the physiological mechanisms that control the FHR before childbirth. We assessed the FHR complexity using three different nonlinear measures namely, time irreversibility (TI), sample entropy (SampEn) and permutation entropy (PE) in 32 fetal recordings, 15 controls and 16 cases.

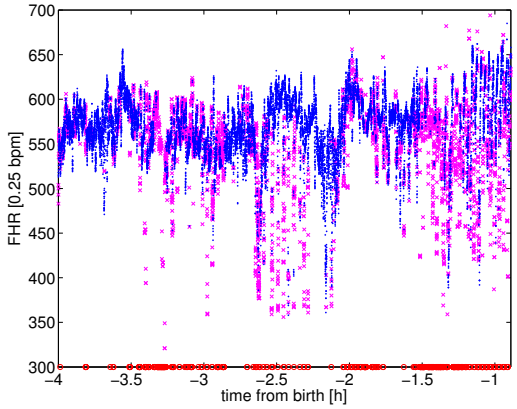
The structure of the paper is as follows. Section 2 describes the nonlinear indices. The dataset and the statistical procedure are detailed in Sections 3 and 4 respectively. Section 5 presents the results. Finally, the conclusions and a brief discussion is presented in Section 6

2. Methods

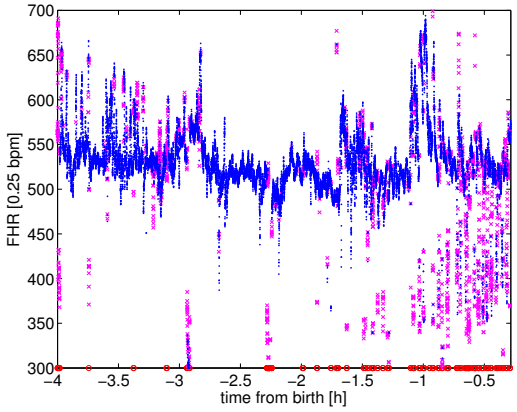
In this section we present a brief description of the nonlinear indices used to assess FHR complexity.

2.1. Permutation Entropy

PE estimates complexity as the entropy of permutations pattern of the elements in a time series. It is a robust method with respect to noise and is easy to compute [8, 9]. Given a time series $x[n]$ for $n = 0 \dots N$, it is embedded into a D-dim space $X = \{x[n], x[n+1], \dots, x[n+D-1]\}$.



(a)hypoxic



(b)control

Figure 1. FHR for (a) a hypoxic and (b) a control fetus. Samples in the FHR are classified by the acquisition machine as: reliable sample, marker "·"; medium reliable, marker "x"; and unrealiable, marker "o".

For a fixed embedding dimension, each vector has associated an ordinal pattern, defined as the permutation $\pi_i = (r_0 r_1 \dots r_{D-1})$ which fulfills [10]

$$x[n + r_0] \leq x[n + r_1] \leq \dots \leq x[n + r_{D-1}]$$

Therefore, there are $D!$ possible ordinal patterns in a D-dimensional embedded space. If $p(\pi_i)$ is the relative frequency of the ordinal pattern π_i, then the PE is defined as the Shannon entropy associated to the distribution of ordinal patterns π_i [9, 10]

$$PE = -\sum_{i=1}^{D!} p(\pi_i) \ln p(\pi_i) \quad (1)$$

2.2. Sample Entropy

Entropy-based methods provide a quantification of the irregularity of a temporal series. Among them, SampEn [11] holds some properties which are appropriate for the study of physiological signals, namely it is robust to noise and outliers, and accordingly, it has been widely applied for characterizing the HRV signal. The SampEn, which is a modification of the Approximate Entropy [12], is the negative natural logarithm of the conditional probability that two sequences which are similar for m points remain similar for $m+1$ points. Thus, a lower value of SampEn indicates more self-similarity in the time series [11]. In order to compute SampEn, the embedded dimension m, i.e., the length of the vectors to be compared, and the noise filter threshold r need to be specified. In this study the values for these parameters are set to $m = 2$ and $r = 0.2$. the standard deviation of the signal, since they are common values used in the literature [12].

Sampen can be estimated as follows

$$SampEn(m, r, N) = -\ln [A^m(r)/B^m(r)] \quad (2)$$

where $A^m(r)$ is the average number of similar (m+1)-dim embedding vectors (within r), and $B^m(r)$ is the average number of similar m-dim embedding vectors (within r).

2.3. Time Irreversibility

Time irreversibility (TI) is related to the unidirectionality of the energy flow across the boundaries of the system. Living beings are systems operating far-from equilibrium, they utilize energy to evolve to and maintain ordered structural configurations, through inherently time irreversible processes. Death can be considered as a state of maximum equilibrium, therefore states approaching death are expected to be more time reversible than those representing far-from-equilibrium healthy physiology [13].

In time series analysis, TI refers to the lack of invariance of the statistical properties of a signal under the operation of time reversal. A method to quantify the degree of TI was presented in [13], it is based on the observation that for a symmetric function the number of increments is equal to the number of decrements. They use this fact for calculating the asymmetry of the original time series and for a number of coarse-grained time series. Consider a time series $X = \{x_i\}, 1 \leq i \leq N$. For scale 1, the time series $Y_1 = \{y_i\}, y_i = x_{i+1} - x_i, 1 \leq i \leq N-1$ is constructed. Then, the difference A_1 between the percentage of increments and decrements is computed according to

$$A_1 = \frac{\sum H[-y_i] - \sum H[y_i]}{N-1} \quad (3)$$

where H is the Heaviside function ($H(a) = 0$ if $a < 0$ and $H(a) = 1$ if $a \geq 0$) and $1 \leq i \leq N-1$. Similarly

	PE	SampEn	TI	STV	$\mathbf{P}_{hf}$
Healthy	0.72 ± 0.04	0.33 ± 0.12	$\mathbf{-0.38 \pm 0.19^*}$	3.23 ± 1.15	0.40 ± 0.18
Hypoxia	0.69 ± 0.07	0.28 ± 0.09	$\mathbf{-0.21 \pm 0.37}$	3.45 ± 1.35	0.43 ± 0.25

Table 1. *Mean±standard deviation of the nonlinear and computed on healthy and hypoxia cases. Symbol * means statistically significant difference (p-value < 0.1) using a bootstrap hypothesis test.*

for scale j, the time series $Y_j = \{y_i\}, y_i = x_{i+j} - x_i, 1 \leq i \leq N-j$ is constructed. Then, the difference A_j between the percentage of increments and decrements is computed according to

$$A_j = \frac{\sum H[-y_i] - \sum H[y_i]}{N-j}, \quad 1 \leq i \leq N-j \qquad (4)$$

The time asymmetry (irreversibility) index is defined as $\sum A_j$ for a pre-defined range of scales. In this study we used $j = 8$ due to the length of the recordings.

3. Data description

FHR records[1] were acquired with a Philips cardiotocograph for a total of 32 recordings, 15 controls and 16 cases in the Hospital Universitario Fundación Alcorcón (Madrid, Spain). A case was declared whether: 1) the PH of the umbilical artery was ≤ 7.05; or 2) the APGAR score was ≤ 7 at 5 minutes after delivery and a reanimation type III or greater was required. The institutional Medical Ethics Review Board approved the use of this data. Figure 1 shows examples for control and hypoxic fetus. For this study we used the last hour of each record before childbirth.

4. Statistical analysis

To test whether exists statistically significant differences on nonlinear indices between controls and cases we performed a statistical hypothesis tests based on bootstrap resampling. The null hypothesis (H_0) represents no difference between controls and cases, against the alternative hypothesis (H_1) that there exists significant differences. For each index we used the mean difference between controls and cases as the statistic to summarize our data. Bootstrap hypothesis test is based on the idea of building an empirical distribution of the statistic, under H_0, and then computing the statistic on B different resamplings. Assuming that H_0 is true, bootstrap statistics are computed on resamplings from a pooled population (control $\cup$ cases). We computed each p-value as the fraction of the points on the distribution (probability) that are more extreme than the actual statistic value [14, 15].

[1]Data is available from the website: http://sites.google.com/site/hufahypoxia.

5. Results

Table 1 shows the mean and standard deviation of the indices computed on healthy and hypoxia cases. Besides nonlinear indices, we also computed short time variability (STV) and high frequency power (PHF) as linear indices, since they are commonly used in the literature. None of the linear indices showed statistical difference between healthy and hypoxia groups.

Figure 2 shows the box plot for the three nonlinear indices comparing healthy and hypoxic fetuses. SampEn free parameters were set to $m = 2$ and $r = 0.15 \cdot std$, which are the usual values in the literature. PE free parameters, embedding dimension, was set to $D = 7$. Finally, TI number of scales was set to $j = 8$.

Entropy indices showed higher complexity (higher values) in healthy fetuses, both SampEn and PE, but without statistical significance. It should be noted that PE showed a reduced standard deviation compared to SampEn and TI, mainly in the healthy group. Healthy fetuses showed TI values farthest from zero than hypoxic fetuses, indicating higher complexity. Applying the bootstrap hypothesis test we verified a statistical significant difference for TI (p-value < 0.1).

6. Discussion and Conclusions

In this work we studied the FHR complexity change due to perinatal hypoxia. The complexity of the FHR was assessed by three different methods, namely: SampEn, PE and TI. The two first estimate the irregularity of a time series, whereas the latter estimates the asymmetry with respect to time reversal. A group of 15 healthy fetuses was compared with a group of 16 hypoxic fetuses. Due to the small number of samples in each group we used a bootstrap hypothesis test to compare both groups.

Healthy fetuses showed higher entropy indices and TI values farthest from zero (p-value¡0.1) than the hypoxic group. These results pointed to a loss of complexity in the hypoxic group. It should be note that PE showed concentrated distributions in both groups.

Nonlinear indices computed on FHR seemed to provided a way to assess the loss of complexity due to perinatal hypoxia, and could be used to provide with a mechanism to early detections of hypoxia.

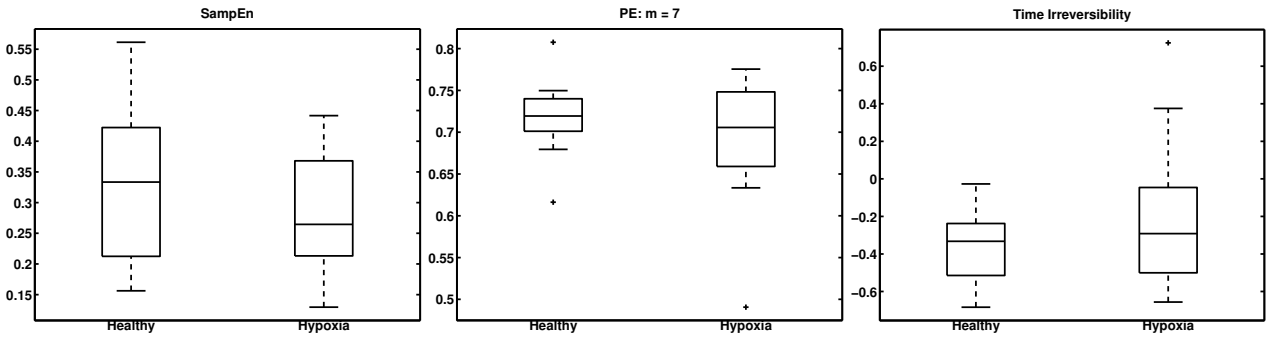


Figure 2. *Boxplot for each of the nonlinear indices, (a) SampEn, (b) PE, (c) TI, comparing healthy and hypoxic groups.*

Acknowledgements

This work has been partially supported by the Research Project from the Spanish Government TEC2013-48439-C4-1-R.

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