31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

Multiparameter Analysis of Heart Rate Variability Signal for the Investigation of High Risk Fetuses

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Abstract— **The purpose of this study is to evaluate the information content provided by the fluximetry information and the analysis of fetal heart rate (FHR) signals, obtained from cardiotocographic recordings, during prenatal monitoring, in a high risk population. The parameters assessed on FHR signals are divided in: (i) time domain parameters (ii) frequency domain parameters, and (iii) the complexity parameters: Approximate Entropy (ApEn), Sample Entropy (SampEn), Multiscale Entropy (MSE), the Lempel Ziv Complexity (LZC) and the Detrended Fluctuation Analysis (DFA). The fetuses were classified as fetal growth restricted (FGR). The results have shown that the FGR fetuses preterm delivered have produced a markedly reduced heart rate variability in respect with those fetuses which were characterized by an alteration in the fluximetric indices. The normal range in cord blood sampling analysis excludes the prolonged hypoxia as a causing factor. Finally, it seems that the residual cardiovascular response in FGR fetuses could be correlated to an alteration in the flow of the main vessels.**

I. Introduction

The umbilical cord blood gas and acid-base assessment are the most objective determinations of the fetal metabolic condition at the moment of the birth. *Asphyxia* may occur in a transient fashion that, although of physiologic interest, has no pathologic sequel. Significant fetal exposure to asphyxia leads to tissue debt, accumulation of fixed acids and a metabolic acidosis. An open question is how to determine whether the asphyxia recognized at delivery may have been present before the onset of labor [1]. This is of particular relevance in preterm infants and in case of fetal growth restriction (FGR).

The term fetal growth restriction describes a decrease in fetal growth rate that prevents a fetus from obtaining his or her complete growth potential. Despite numerous approaches to managing FGR, there are no effective therapies to improve growth pattern of a fetus, so prenatal management is aimed primarily at determining the ideal timing and mode of delivery [2]. This assessment must be individualized, depending on several variables: gestational age of the fetus, maternal health, severity of the FGR and fetal wellbeing. Perhaps optimizing the delivery time and removing the fetus from a suboptimal environment can prevent risk of hypoxia and significant morbidities. Thus new methods for fetal surveillance has been proposed in order to identify the pathophysiology in the pregnancies at risk. The use of Doppler Velocimetry have permit to evaluate the placental-fetal circulation and to assess the level of fetal oxygenation [3]. In particular pregnancies with absent or reverse end-diastolic flow have been associated with high perinatal mortality rates [4].

The purpose of the study is to evaluate the information content provided by the fluximetry information and the analysis of fetal heart rate (FHR) signals, obtained from cardiotocographic recordings, during prenatal monitoring. The cardiotocography (CTG) is the most common ante partum monitoring technique and it is based on the detection of fetal heartbeats by Doppler Ultrasounds. Preliminary results are presented.

II. Methodology

A. Data Collection

We analyzed FHR signals recorded by a CTG monitor HP M1351A during antepartum period. Each recording length takes on average more than 40 minutes. We've selected 6 subjects for a total of 25 CTG recordings performed before the delivery, between the 28th and 34th gestational week (g.w.). The fetuses were all classified as FGR according to the biophysical profile and they were premature delivered by a caesarian section (before the 34th gestational week). For all the subjects a cord blood sampling was performed at the delivery, in order to exclude the presence of prolonged hypoxia and thus to ensure the prompt intervention. In fact, all the fetuses have reported values in the normal range of pH, pCO_2, base excess, buffer base in the umbilical artery or vein.

The subjects were divided into two groups according to the presence/absence of Doppler Velocimetry alterations. Group 1 is constituted by 4 subjects (13 recordings) which are premature delivered because the presence of some alterations in the fluximetric indices. Group 2 is constituted by 2 subjects (12 recordings) premature delivered because of a reduced HRV without a significant variation in the Doppler velocimetry analysis (see Table I).

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TABLE I

FETAL DATA FOR EACH SUBJECT

Are reported the gestational week (g.w.) of the fetus at the moment of delivery, the weight of the newborn (g), if the newborn went to the intensive care unit (ICU) and the description of the fluximetric alteration (u.a.=umbilical artery; dv=ductus-venosus)

	delivery g.w.	newborn weight (g)	ICU	Fluximetry
Subject 1	31	1400	no	Reduction in u.a. end diastolic flow
Subject 2	31	760	yes	u.a. and dv regular
Subject 3	31	970	yes	Reduction in u.a. end diastolic flow
Subject 4	34	1450	yes	u.a. and dv regular
Subject 5	31	670	yes	u.a. reverse end diastolic flow, reduction in dv end diastolic flow
Subject 6	30	1300	yes	Absence of u.a. end diastolic flow and reduction in dv end diastolic flow

B. Data Analysis

As the CTG signal often appears corrupted by a large amount of noise, artifacts, or even signal loss, it was introduced a quality index. In the HP-M1351A, the quality index quantifies three different levels of the FHR signal: optimal (green), acceptable quality (yellow), and insufficient quality and/or signal unavailable (red). The evaluation is based on the output of the autocorrelation procedure upon which the recording of FHR signal is based [5]. For all recordings a standard analysis procedure was carried out through the identification of the baseline, the detection of accelerations and decelerations.

The parameters assessed in this study are divided in: (i) time domain parameters (ii) frequency domain parameters, computed by adopting a power spectral estimation based on the parametric approach, and (iii) the complexity parameters. The time domain parameters are: mean value, DELTA, Short Time Variability (STV), Long Term Irregularity (LTI) and Interval Index (II) [5][6].

As frequency domain parameters we considered the power content and percentage of the following frequency band range: the Low Frequency (LF)component range (0.04-0.15Hz), Middle Frequency (MF) power (0.15-0.5Hz, not present in adult human subjects), High Frequency (HF) power (0.5-1.0Hz), the LF/(MF+HF) ratio.

The complexity indices used in this study are: Approximate Entropy (ApEn) [7], Sample Entropy (SampEn) [8], Multiscale Entropy (MSE) [9], the Lempel Ziv Complexity (LZC) and the Detrended Fluctuation Analysis (DFA) [10].

The time domain and frequency domain parameters, ApEn, SampEn and LZC were estimated on 360 or 120 point long sequences as described in [5,6]. The HR signal was corrected before the analysis and the signal subsets with insufficient quality were excluded from the parameter estimation procedure, i.e. the signal chunks containing zeros were excluded from the analysis (0 is the value that the HP monitor attributes when the signal is unavailable or the preprocessing procedure judges it unacceptable; it has no physiological meaning). The evaluated index was the mean value of parameters computed on the intervals.

The indices of two groups were compared by means of t-test and Wilcoxon rank-sum test. The significance was considered when the index passed both tests with a P-value<0.05.

C. Lempel Ziv Complexity and Coding Procedure

The measure of complexity introduced by Lempel and Ziv assesses the so-called algorithmic complexity, which is defined according to the Information Theory as the minimum quantity of information needed to define a binary string. In case of random strings, the algorithmic complexity is the length of the string itself. In fact any compression effort will produces an information loss. The LZC quantifies the rate of new patterns arising with the temporal evolution of the signal. The algorithm to assess LZC is fully described in [6]. The adopted measure of complexity is normalized by a factor depending on the sequence length. This permits to compare the complexity values of two strings different in length. In order to estimate the LZC for a biological signal, it is necessary to transform the time series into symbolic sequences. In this work we considered two different approaches. As suggested in [11], the most straightforward procedure is to use the simple increase/decrease of the signal.

Given a signal $\{x_n\}$, the encoding rule adopted for the *binary* alphabet is the following: we assign 0 if $x_n \leq x_{n-1}+p\cdot x_{n-1}$, and 1 if $x_n>x_{n-1}+p\cdot x_{n-1}$. The rule for the *ternary* alphabet is: 2 if $x_{n-1}-p\cdot x_{n-1}\leq x_n\leq x_{n-1}+p\cdot x_{n-1}$, 0 if $x_n<x_{n-1}-p\cdot x_{n-1}$ and 1 if $x_n>x_{n-1}+p\cdot x_{n-1}$. The factor p is a fixed percentage: the current value is then classified as stationary if it lies in a p range around the previous sample. This procedure is proposed to limit the effect of additive noise and to exclude the dependence on signal quantization. For these analyses we adopted the encoding parameter p=0.05 both for the binary LZC(2,p) and ternary coding LZC(3,p).

D. Multiscale Entropy

The Multiscale Entropy (MSE) was proposed in order to capture HRV fluctuations at different degrees of resolution, i.e. in a multiscale manner. The first step to compute MSE is the construction of the coarse-grained time series. For each of these new time series, an entropy measure is calculated and the obtained value is plotted as a function of the coarse-graining scale factor [9]. Given a discrete time series

$\{x_1,\ldots,x_n\}$, the series $\{y^{(\tau)}\}$ are constructed as a function of the scale factor τ as follows:

$$y_j^{(\tau)} = \frac{1}{\tau}\sum_{i=(j-1)\tau+1}^{j\tau} x_i \text{ , for } \quad 1 \le j \le \frac{N}{\tau} \qquad (1)$$

The length of the current series is the ratio between the length of the original series and τ. For τ=1, the series $\{y^{(1)}\}$ is simply the original one. The adopted estimators for the MSE analysis were the Approximate Entropy (ApEn) [7] and the Sample Entropy (SampEn)[8]. The parameters adopted for the computation of ApEn and SampEn are: m=1 and r=0.1, m=2 and r=0.15 and 0.2 and the scale factors analyzed range from 1 to 15. The time series were constituted by the first 4000 samples, which correspond to about 30 minutes.

E. Detrended Fluctuation Analysis

The DFA can be simply defined a modified root mean square analysis of a random walk. Briefly, the time series to be analyzed is firstly integrated. Next, the integrated time series is divided into boxes of equal length, n. In each box of length n, we estimate a least squares line which fits the data (representing the *trend* in that box). Next, we detrend the integrated time series by subtracting the local trend in each box.The root-mean-square fluctuation $F(n)$ of this integrated and detrended time series is calculated. This computation is repeated over all time scales (box sizes) to characterize the relationship between $F(n)$, the average fluctuation, and the box size. A linear relationship on a log-log plot indicates the presence of power law (fractal) scaling. Under such conditions, the fluctuations can be characterized by a scaling exponent υ, the slope of the line relating log $F(n)$ to log n [10]. The time series were constituted by the first 4000 samples, which correspond to about 30 minutes. The results show that the crossover is always present and thus two scaling slopes were considered: the short-term scaling slope υ_1 (n<76, 38s) and the long-term scaling slope υ_2 (n>76, 38s).

III. RESULTS

The time domain and entropy parameters have shown significant differences. The FGR fetuses without fluximetry alterations (Group 2) present an important decrease of heart rate variability both in terms of amplitude (LTI, DELTA, STV) and regularity (all the entropy estimators resulted significant lower) in respect with the values obtained for the Group 1. All spectral components are significant lower as well, as table II shows.

The reduced complexity of the HRV signal in Group 2 is demonstrated also in the lower values of MSE (figure 2) which . All the entropy estimators resulted significant.

Furthermore, the DFA provided significant higher values of long term scaling slope in Group 2 (1.260±0.159) than Group1 (0.921±0.148). Notice that the long term scaling slope greater than 1 has been observed to be associated to a pathological condition in the adult [10][12].

In order to investigate the possible connection with the different type of fluximetric indices, we've compared amongst the CTG recordings of Group 1, those with alterations in the flow of ductus-venosus and those with alterations in the umbilical artery (respectively 8 and 5 recordings). In this case we have found no significant differences in none of the indices considered in this study (see an example in figure 4). This would confirm the homogeneity of the Group 1.

TABLE II
Values obtained from CTG recordings for both groups (avg±std). The symbol † refers to indices resulted significant

	mean (msec)	VLF (ms^2) †	LF (ms^2) †	MF (ms^2) †	HF (ms^2) †	LF/(MF+HF) †
Group 1	311.37±104.67	93.11± 83.13	61.04± 46.16	5.36± 3.97	5.73±4.14	4.23±1.89
Group 2	257.40±61.35	38.46±22.71	14.07±11.73	1.68± 1.35	1.37±0.88	2.79±1.03

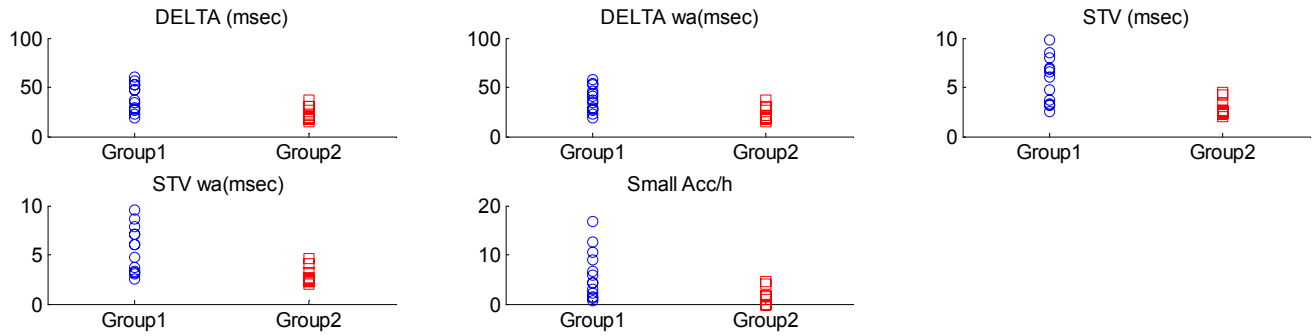

Fig. 1: The figure shows the values assessed for each recordings of both groups. The indices resulted significant different (P-values<0.05) and these are: DELTA, STV, DELTA and STV assessed without considering accelerations (w.a.), small accelerations normalized per hour.

IV. Conclusion and Discussion

The analyses have shown that some cases of FGR fetuses preterm delivered produced a markedly reduced heart rate variability, which was not accompanied by an alteration in the fluximetric indices (Group 2). The normal range in cord blood sampling analysis excludes the prolonged hypoxia as a causing factor, and it assures that a prompt intervention has been performed in response to a life-threatening condition of the fetus. The resulted homogeneity of Group 1 suggests that the HR response is not dependent on the vessels which were affected by the fluximetric alteration. This would be explained by the fact that we are dealing not with hypoxic or metabolic acidotic fetuses.

In particular, it seems that the residual cardiovascular response in FGR fetuses could be correlated to an alteration in the flow of the main vessels. The reduced HRV of the FGR fetuses without these alterations could be explained by a pathological condition, not associated however to a prolonged hypoxia.

The limitation of this study is surely the small number of subjects, however it has raised several questions which have not been already addressed: e.g. is always a life-threatening condition accompanied by an alteration of fluximetric indices? is it always associated with hypoxia?

The answer of these question surely will improve the clinical and diagnostic process.

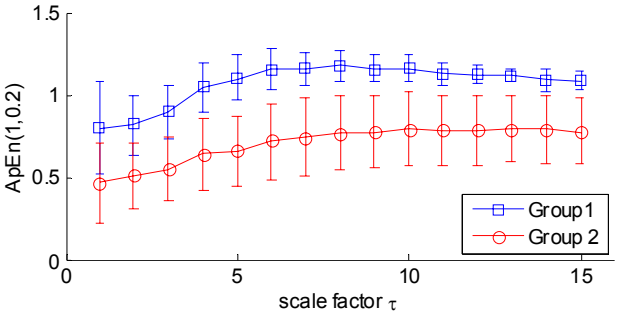

Fig 2: MSE values (avg±std) assessed for the two groups.

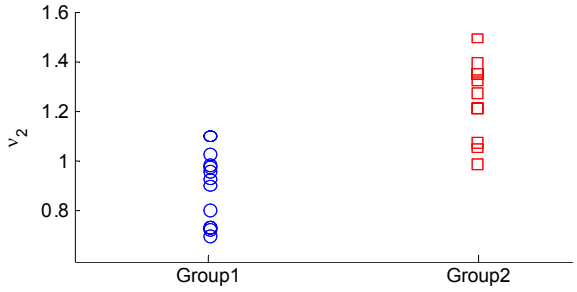

Fig. 3: Values of the long term scaling slope computed for each recording for the two groups.

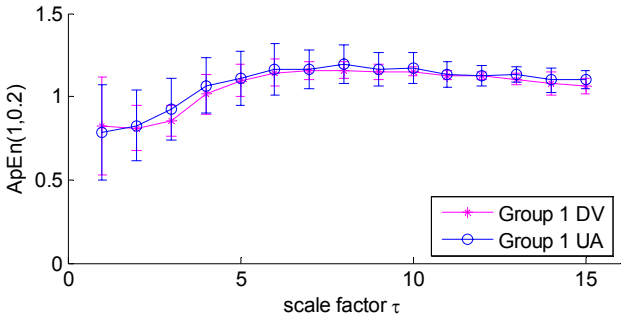

Fig 4: MSE values (avg±std) assessed for the two subgroups of the Group 1: CTG recording of fetuses with alterations in the flow of ductus-venosus (DV)and those with alterations in the umbilical artery (UA).

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