HRV Descriptors for Fetal Distress Assessment in Pregnancy with Fetal Growth Restriction

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Abstract - *This paper focused on the fetal wellbeing assessment, through the selection of HRV descriptors as evident markers of fetal distress. The study of behavior in experiments with control groups of healthy pregnant women and pregnant women with fetal growth restriction allows obtaining quantitative descriptors that help assess the loss of fetal well-being. The results show that SI (Sp=1, Se=0.9882), and AMo (Sp=0.8118, Se=0.9882) are evident markers of fetal distress*.

Keywords: Heart Rate Variability, Fetal Growth Restriction, Fetal well-being

1 Introduction

Electronic fetal monitoring is an important part of the prenatal surveillance system that contributes to the best perinatal outcome. Its objective is to assist in the correct diagnosis of fetal well-being. However, the lack of precision of several fetal monitoring methods is well known [1]. Cardiotocography (CTG) methods have been a standard despite the lack of evidence about reduces the adverse sequelae of neurodevelopment, including neonatal hypoxic-ischemic encephalopathy and cerebral palsy. This method has a high rate of false positives and poor inter- and intra-observer reliability [2-4], such that fetal status and the perinatal outcome cannot be predicted reliably.

CTG is a method based on cardiac rhythm reactivity to fetal intrauterine motor activity in the prenatal period. However, CTG-based techniques require prolonged ultrasonic monitoring. CTG demonstrates the response of the sinus node to the continuous interaction of the sympathetic and parasympathetic tones of the autonomic nervous system [5,6].

Autonomic control of fetal cardiac rhythm could be investigated by fetal heart rate variability (HRV). HRV captures the impact of central and peripheral circuits on regulation in hemodynamics [7]. The fetal HRV parameters exhibit a wide range, even under normal conditions. The peculiarities of the fetal neurobehavioral response in the active and sleepy periods may complicate the interpretation of the conventional CTG tracing and increase the level of cesarean interventions [8-10].

Recent research has explored different biochemical and biophysical markers, as well as the correlation between maternal-fetal hemodynamic processes, to understand better the complex processes involved in the loss of fetal well-being [11]. The early identification of a pathological state is fundamental to predict possible complications and to take appropriate decisions.

In growth restricted fetuses, the etiologies are not yet identified and the known associations involve fetal, placental and/or maternal factors. The fetus is at risk of hypoxia and this condition is often associated with increased perinatal mortality and morbility [13]. This paper presents results obtained of analysis of the main fetal HRV parameters in patients with normal fetal development and fetal growth restriction (FGR).

2 Materials and Methods

For the development of this work were used the records of 49 pregnant women in the department of maternal and fetal medicine of Kharkiv, municipal perinatal center. Inclusion criteria: FGR according to ultrasonography. The FGR was in diagnosed in case of fetal weight parameters were lower than 10th percentile [14]. Exclusion criteria: multiple pregnancy, severe pre-eclampsia, preexisting medical disorders like diabetes mellitus, metabolic syndrome, cardiac diseases, renal disease, thyrotoxicosis. These records were divided into four groups: group I of healthy pregnant women without loss of fetal well-being. Group II of healthy pregnant women with loss of fetal well-being or fetal distress. Group III of pregnant women of high-risk type III without loss of fetal well-being and Group IV of pregnant women of high-risk type III with loss of fetal well-being. The fetal HRV parameters were obtained with the fetal noninvasive computer electrocardiographic system "Cardiolab Baby Card" equipment (Scientific and research center "KhAI Medica", Ukraine) [1, 11, 12]. The sampling rate was 1kHz. For all cases reported, the study protocol was approved by the Bioethics Committee of the Kharkiv Medical Academy of Postgraduate Education, (registration number 0105U002865).

For the development of this study records were organized in two groups, controls and fetal distress. In order to select the best descriptors, were made statistical analysis of relationship between HRV parameters shown in Table I and clinical fetal

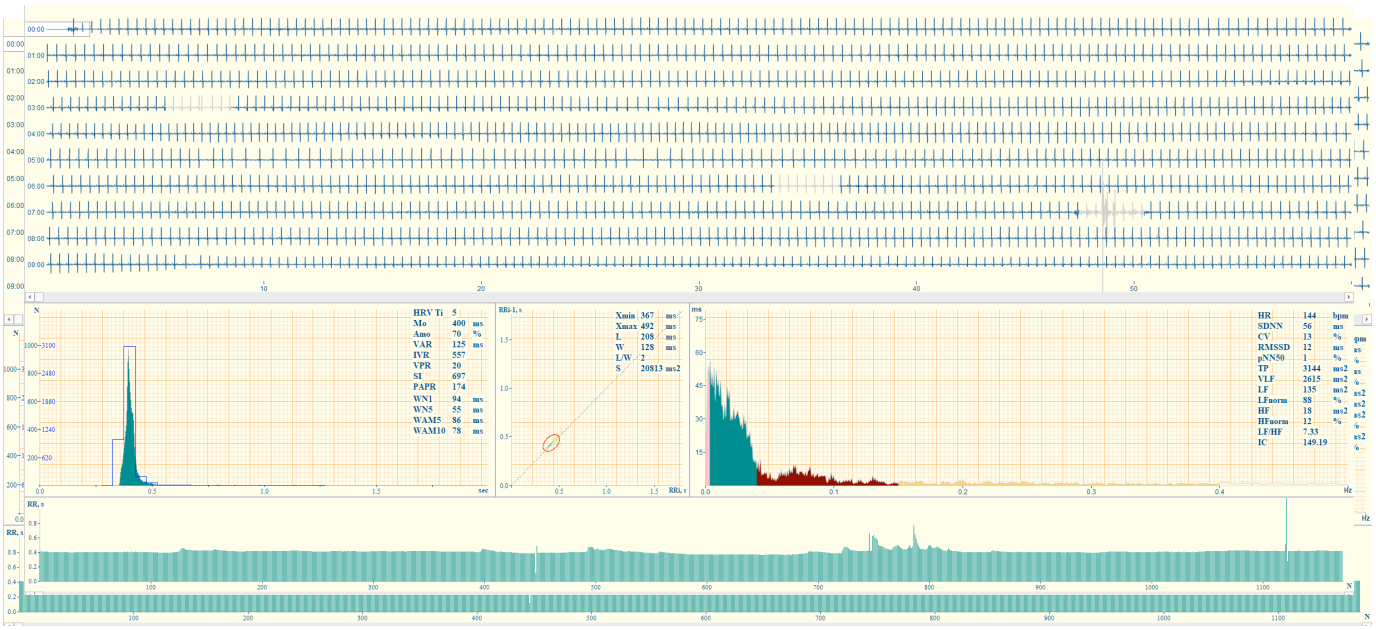

Fig. 1 fetal HRV CardioLab analysis results

distress. The data was analyzed in MatlabTM, on the values obtained from Cardiolab. An example of Cardiolab HRV data window is shown in figure 1. The values measurement in observed patients with healthy pregnancy and pregnancy with fetal distress are shown in Table II. From the ROC analysis, were obtained the specificity (*Sp*) and the sensitivity (*Se*) of the parameters concerning the fetal well-being. *Sp* and *Se* are given by equations (1) and (2) respectively:

$$S_p = \frac{VN}{VN + FP} \tag{1}$$

where, *VN* are the True Negatives and *FP* are the False Positives

$$S_e = \frac{VP}{VP + FN} \tag{2}$$

where, *VP* are the Positive Truths and *FN* corresponds to the Negative False. The Pearson´s and Spearman´s correlations coefficients (ρ) between HRV variables and fetus status was calculated respectively as:

$$r = \frac{\sum_{i=1}^{n}\left(x_i - x\right)\left(y_i - y\right)}{\sqrt{\left[\sum_{i=1}^{n}\left(x_i - \bar{x}\right)^2\right]\left[\sum_{i=1}^{n}\left(y_i - \bar{y}\right)^2\right]}} \tag{3}$$

where x_i and y_i are the values of HRV parameter and Clinical diagnosis for the *i-th* individual.

$$rs = 1 - \frac{6\sum_{i=1}^{n} d_i^2}{n\left(n^2 - 1\right)} \tag{4}$$

where d_i is the difference in ranks for each HRV parameter and clinical diagnosis.

Table I.
Fetal HRV parameters

Index	Definition
SDNN, ms	Standard deviation of normal to normal intervals
RMSSD, ms	Root mean square of successive heartbeat interval differences
pNN50, %	Proportion of the number of pairs of NNs differing by more than 50 ms divided by the total number of NNs
AMo, %	Mode Amplitude (the most frequent value of NN interval of the highest column in the histogram
SI, conv. un.	Stress Index
TP, ms^2	Total Power
VLF, ms^2	Very low frequency
LF, ms^2	Low Frequency
HF, ms^2	High Frequency

Table II. Fetal HRV variables in the study population

Index	Healthy	Distress
SDNN	15 – 142	7 – 50
RMSSD	6 – 56	2 – 26
pNN50	0 – 32	0 – 9
SI	63 – 1446	406 – 3040
AMo	20 – 89	61 – 100
TP	200 – 19683	39 – 2242
VLF	69 – 16511	6 – 1073
LF	31 – 3189	9 – 468
HF	15 – 1227	1 – 300

3 Results

The Area Under Curve (AUC) of ROC analysis is shown in figure 2. As can be seen, the parameters with the largest AUC were SI (0.9956) and AMo (0.917). The smallest AUC was obtained for pNN50 (0.7982). These results correspond to the highest *Sp* and *Se* for SI and AMo, and the lowest for pNN50. Table III shows the statistical results with ROC, Pearson, and Spearman tests, the significance was set at p-value <0.01.

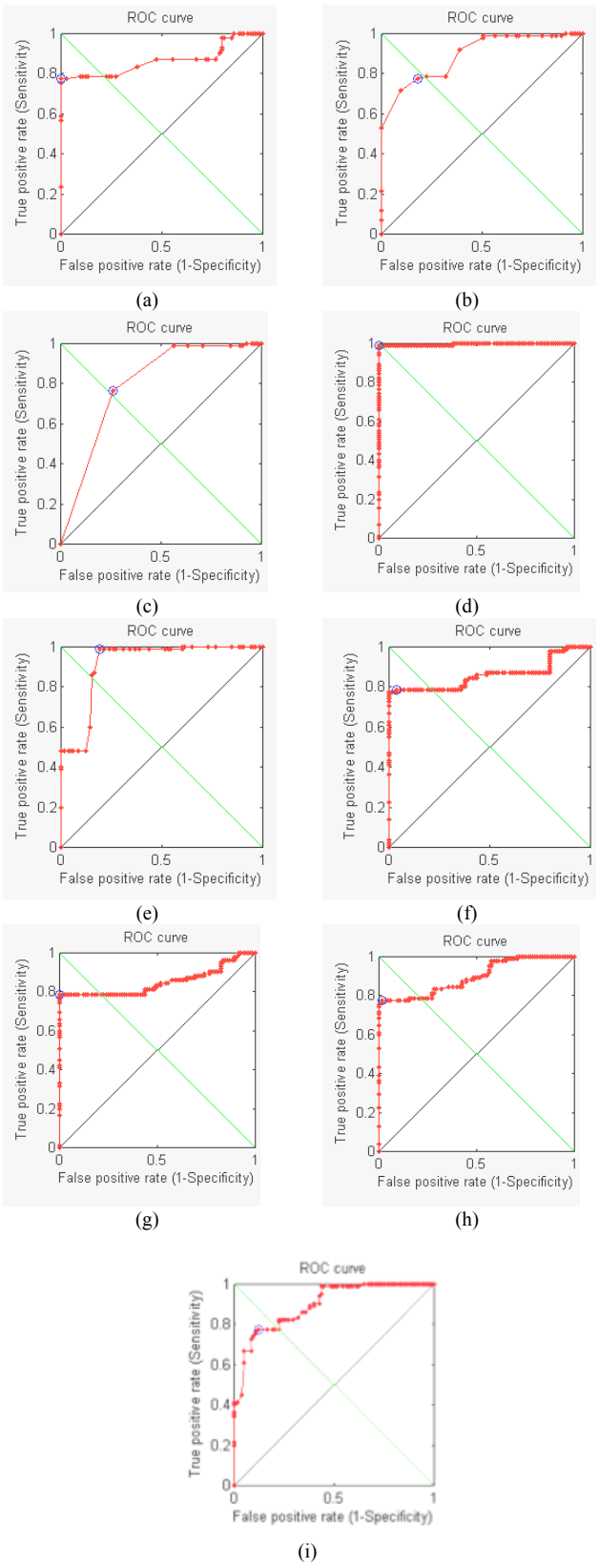

Fig 2. ROC for HRV variables. a) SDNN AUC=0.8653, b) RMSSD AUC=0.8922, c) pNN50 AUC=0.7982, d) SI AUC=0.9956, e) AMo AUC=0.917, f) TP AUC=0.8614, g) VLF AUC=0.8514, h) LF AUC=0.898, i) HF AUC=0.8976

Even though SDNN and TP have a high specificity: SDNN (Sp=1) and TP (Sp=0.9647), both parameters have low sensitivity: SDNN (Se=0.7765) and TP (Se=0.7882). Low sensitivity of SDNN and TP were expected because the autonomic tone has a weak correlation with fetal distress.

On the other hand, SI shows Se = 0.9882 and Sp = 1 and AMo presents Se = 0.9882 and Sp = 0.8112, what is consistent, since SI and AMo are independent of the stationary fetus state. The Pearson´s correlation for SI and AMo were 0.9265 and 0.7204 respectively. Spearman´s correlation were 0.8585 and 0.7243 for SI and AMo, respectively.

HF related to vagal tone has Se = 0.7765 and Sp = 0.8824 and LF related to sympathetic tone presents Se = 0.7765 and Sp = 0.9882.

SI and AMo can be considered as good descriptors from the results shown in Table III, because their cutoff point showed better Se and Sp (values close to 1), and the Pearson´s and Spearman´s correlations are positive and maximum, as can be seen in figure 3.

Table III.
ROC and correlations analysis of fetal HRV parameters

Descriptor	Se	Sp	ρ - Pearson	ρ - Spearman
SDNN	0.7765	1	-0.5376	-0.6352
RMSSD	0.7765	0.8235	-0.533	-0.6826
Pnn50	0.7647	0.7412	-0.3623	-0.5612
SI	0.9882	1	0.9265	0.8585
AMo	0.9882	0.8118	0.7204	0.7243
TP	0.7882	0.9647	-0.2513	-0.6262
VLF	0.7882	1	-0.1949	-0.6089
LF	0.7765	0.9882	-0.4209	-0.6895
HF	0.7765	0.8824	-0.4169	-0.6894

Fig 3. Results of ROC analysis, Pearson and Spearman correlations for fetal HRV parameters.

4 Conclusions

Fetal HRV captures the continual changes of the autonomic (sympathovagal) balance. The results obtained show that the parameters of the HRV can be markers that allow to differentiate the well-being fetus status, in the case of FGR.

The HRV parameters were evaluated by *Sp*, *Se*, and Pearson´s and Spearman´s correlation analysis. SI showed *Se* = 0.9882, *Sp* = 1, ρ–Pearson=0.9265 and ρ–Spearman = 0.8585. AMo presented *Se* = 0.9882, *Sp* = 0.8118, ρ–Pearson=0.7204 and ρ–Spearman = 0.7243. These results are consistent since they are independent of the fetal stationary state. The high *Sp* and *Se* obtained by SI and AMo, are consistent with results of Pearson´s and Spearman´s correlations, so that these parameters can be considered as evident markers of fetal well-being status.

Since SI and AMo are relevant to the sympathetic part of the autonomic regulation the opinion on the involvement of the sympathetic mechanisms in fetal distress is supported [1]. The predictive value of the parasympathetic regulation variables was lower. The growing activity of this division of the autonomic function is a marker of fetal neurological maturation [5]. The relation found between maternal and fetal HRV parameters was a sign of fetal and maternal coupling in healthy pregnancy. Maternal respiratory sinus arrhythmia was speculated as a reason of this regularity. It was disturbed in pre-eclampsia [11]. Fetal growth is known to be impacted by maternal organism [6, 13]. The investigation of the possible relations between maternal and fetal HRV and its fractal components will create a novel concept of the management of women with growth-restricted fetuses.

Formerly, the most sensitive and specific for fetal distress T/QRS ratio obtained from fetal non-invasive ECG tracing was found [1, 12]. Since peaks and intervals are detectable on fetal averaged PQRST complex the subsequent investigation of their clinical significance is of great prospect. But the study population of the above-mentioned research was suffered from pre-eclampsia. Thus, pre-eclampsia could change fetal cardiac conductivity. But will T/QRS ratio be of use in diagnosing fetal distress among all pregnant women is still a question?

The main criterion of fetal well-being is a reactivity to its motile activity by accelerating of the heart rate during non-stress test [2, 3]. The obtained results could make it possible to think that SI and AMo will become an alternative to the Dawes-Redman criteria. The assessment of short-term variations (STV) and long-term variations (LTV) was found to be of use in diagnosing of fetal compromise. These variables used in CTG monitors are known as the most evident markers of fetal distress [4, 9]. But the duration of the recording should be not less than 1 hour or, at least, 30 minutes. This time interval is known to be associated with better sleep/awake fetal status ratio [2, 4]. Therefore, the application of the proposed fetal HRV variables will help to use fetal non-invasive ECG tracing of the only 10 minutes long. It will be more convenient in clinical practice. Another advantage is the possibility to support or neglect fetal distress in case of negative (areactive) or false-negative non-stress test.

The hypothesis of the intrauterine programming of the diseases determines that any abnormalities during fetal life will have a subsequent clinical manifestation afterward. The cardiac signals proceeding is a convenient approach to the assessment of fetal autonomic maturation [6, 13]. Fetal HRV variables are disturbed in growth-restricted fetuses. Therefore, the investigation of fetal neurobehavioral response in case of intrauterine growth restriction is a possible way for the fetal well-being screening. But fetal growth restriction is not always associated with fetal distress and still stimulating obstetrical aggression in its projections on the term and the mode of delivery. That is why the outcome of our research in future is an advanced protocol of management of pregnant women with fetal growth restriction.

The findings of this work is based on fetal non-invasive ECG investigation. This method is still a challenge for the clinician [9]. The main problem is a low signal to noise ratio [1]. But fetal non-invasive ECG could be used for fetal Holter monitoring. The possibility for the creation of the system for fetal wireless distant monitoring will contribute to the better diagnosing of fetal compromise and cardiac arrhythmias.

HRV descriptors can be used in an assessment system, for discrimination or prediction between fetuses with loss of fetal well-being and normal fetuses, both in pregnancies with intrauterine growth restriction and pregnancies of healthy fetuses.

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