Maturation of Fetal Cardiac Autonomic Control as Expressed by Fetal Heart Rate Variability

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Abstract

The objective of this study was to establish quantitative parameters for estimating the fetal Autonomic Nervous System (ANS) maturation, derived from the Fetal Heart Rate (FHR) variability.

A Fetal ECG was non-invasively obtained by extraction from the maternal abdominal ECG signal, which allowed for beat-to-beat detection of the fetal heart beats. 35 healthy pregnancies were examined and divided into three groups according to gestational age. FHR variability was analyzed by a time-frequency decomposition based on a Continuous Wavelet Transform (CWT).

The results imply that the fetus undergoes a neural organization during the last trimester of pregnancy and that the sympatho-vagal balance is gradually reduced with the gestational age.

1. Introduction

Investigation of the maturation of fetal cardiac autonomic control is an important component for understanding the development of the neural and cerebral system of the fetus.

For fetal autonomic control to be effective, a certain level of maturation of both the afferent and efferent divisions of the Central Nervous System is required, as is innervation of the cardiac tissue. Furthermore, these nerves must be able to generate active neurotransmitters, and the effector organ must have suitable receptors that will enable it to react to these neurotransmitters. In addition, the sympathovagal neural activity must be synchronized and integrated by the sinus node in order to achieve the reciprocal effect of increasing or decreasing the FHR. As a result, we would expect to see more efficient ANS modulation of the HR at relatively advanced stages of pregnancy.

The correlation between fetal body movements and FHR increases with gestational age. Near the end of pregnancy this correlation becomes highly significant, and FHR accelerations are visible in parallel to the fetal body movements [1,2].

Additionally, there is evidence of modulation of the FHR during periods of fetal respiratory movements [3]. Fetal respiratory movements are faster than those of adults varying between, and at times exceeding, 30 to 90 movements per minute.

HR fluctuation analysis allows for a non-invasive estimation of fetal autonomic control. A study of the periodicities of these fluctuations enables a non-invasive study of both the sympathetic and parasympathetic branches of the ANS. Hence, one can observe all of the Heart Rate Variability (HRV) frequency components by applying a frequency-domain approach.

Since the heart's response to parasympathetic stimulation is almost instantaneous, spectral analysis techniques require a very accurate detection of fetal heart beats [4].

Only few technologies, which can achieve this required beat-to-beat accuracy, are available. Most of them are based on fetal magnetic heart signals [5,6].

In the past, our Medical Physics group has developed a unique and complex algorithm for on-line Fetal ECG (FECG) detection [7]. The FECG is non-invasively obtained by extraction from the maternal abdominal ECG signal, and allows for beat-to-beat detection of the fetal R-waves. This enables us to produce a very accurate instantaneous FHR signal.

The goal of this study presents a non-invasive method to assess the fetal ANS activity. This approach has been applied at different gestational ages in order to estimate the fetal ANS maturation.

2. Methods

2.1. Fetal population

35 healthy pregnancies were examined and divided into three groups according to gestational age (Table 1).

No fetal or maternal pathology was observed in any of the 35 cases up to the moment of abdominal ECG recording. There were no early births (Average birth time: 39.5±0.9 weeks), and in all cases fetal weight at birth met the normal curve (Average weight at birth: 3370±420 gr). The study was approved by the Ethical Committee of Beilinson Medical Center. All subjects signed a written informed consent form.

Table 1. The three gestational age groups

Group Number	Number of Subjects	Mean gestational age [weeks ± SD]	Mean duration of recording [minutes ± SD]
1st Group: Middle of second trimester	10	23±2	13±2
2nd Group: Beginning of third trimester	10	32±1	16±6
3rd Group: End of third trimester	15	39±1	24±10

2.2. Data acquisition

The recordings were conducted with the aid of a Fetal ECG and Heart Rate Monitor (FEMO) system, a device based on an algorithm developed by the Medical Physics group at Tel Aviv University [7]. The FEMO is a rapid computer based non-invasive system which detects the superimposed maternal and fetal ECG signal from the mother's abdomen, and then separates and processes the two signals independently. The application requires only a single lead with three electrodes, and runs on-line on a PC with an A/D converter (sampling rate 300Hz).

In each case, the electrode configuration was determined by the optimal signal to noise ratio. During the processing procedure, a visual validation of the detection of fetal QRS complexes was performed.

2.3. Signal processing

A CWT was used to assess the time-dependent power spectrum of FHR fluctuations. The CWT maps the one-dimensional time dependent signal into a two-dimensional frequency-time plane [8].

An important characteristic of the CWT is its variable resolution. In the low frequency range the CWT provides high resolving power between adjacent frequencies, with low resolution in the time domain. In the high frequency range the situation is reversed – the high resolution is in the time domain, while the resolution in the frequency domain is low.

An accurate selection of the Low Frequency (LF) and the High Frequency (HF) ranges allowed the creation of dynamic parameters for the estimation of the fetal autonomic states. Integrating the CWT power density over the appropriate frequency bands allows examining the change in each relevant frequency band as a function of time. Another dynamic parameter is the ratio between the LF band and the HF band, which might (as in adults) reflect the sympatho-vagal balance as a function of time.

2.4. Statistics

One-way ANOVA, along with post-hoc testing (Tukey), was applied for the comparisons between the groups mean power values. Groups were considered as different when the p value was < 0.05. When necessary, the power values have been modified (square root) to improve the normality of the distribution.

3. Results

The FHR spectral analysis results for all 35 fetal cases where abdominal ECG was recorded were examined. The example in Figure 1 shows the FHR analysis results of a 38 week old fetus.

Figure 1 is an example for the signal processing procedure that was carried out for all 35 cases examined. In all cases a similar pattern of spectral distribution was observed.

Figure 2 summarizes the average values of the power integrals calculated for each of the examined cases. These values were divided into three groups based on the gestational age (Table 1).

In both the VLF and LF domains (Figure 2, Graphs A and B respectively) there was a significant difference between the average values of the power integrals in the three age groups ($p<0.05$). An analysis of the source of difference between the age groups showed that in both the VLF and LF domains the average values of group 1 were significantly lower than those of group 2. The difference between groups 2 and 3 was, in both cases, less significant.

In the HF domain (Figure 2, Graph C) the average values of the power integrals increased significantly with gestational age ($p<0.05$).

The average value of both the VLF/LF and the VLF/HF ratios decreased significantly with gestational age ($p<0.05$; Figure 2, Graphs D and E respectively). In Graph D, the average values of group 1 were significantly higher than these values in groups 2 and 3. In Graph D there was not a significant power difference between groups 1 and 2, but the power in group 3 was reduced.

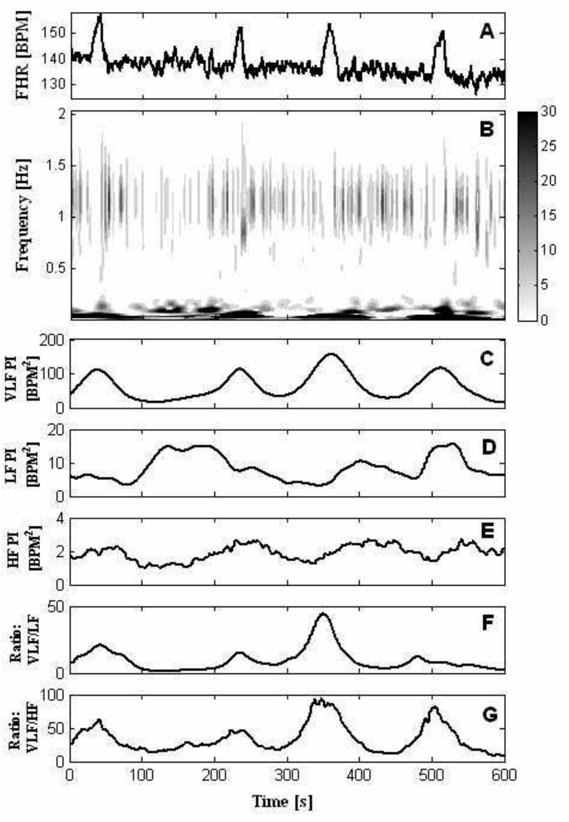

Figure 1. Spectral analysis of fetus at 38 weeks

A) Instantaneous FHR. 600 seconds recording.

B) Mapping of the power spectrum after a CWT of the FHR. X Axis – time, Y Axis frequency and Z axis (grayscale) - the power spectrum.

C) VLF power integral as a function of time. Frequency range: 0.01-0.08Hz. There is a distinct increase of power corresponding to the FHR accelerations.

D) LF power integral as a function of time. Frequency range: 0.08-0.2Hz.

E) HF power integral as a function of time. Frequency range: 0.4-1.5Hz. An average filter with a window of 15 seconds was employed on the HF power integral to allow for comparative analysis between the HF, LF and VLF power integrals.

F) VLF/LF ratio as a function of time.

G) VLF/HF ratio as a function of time.

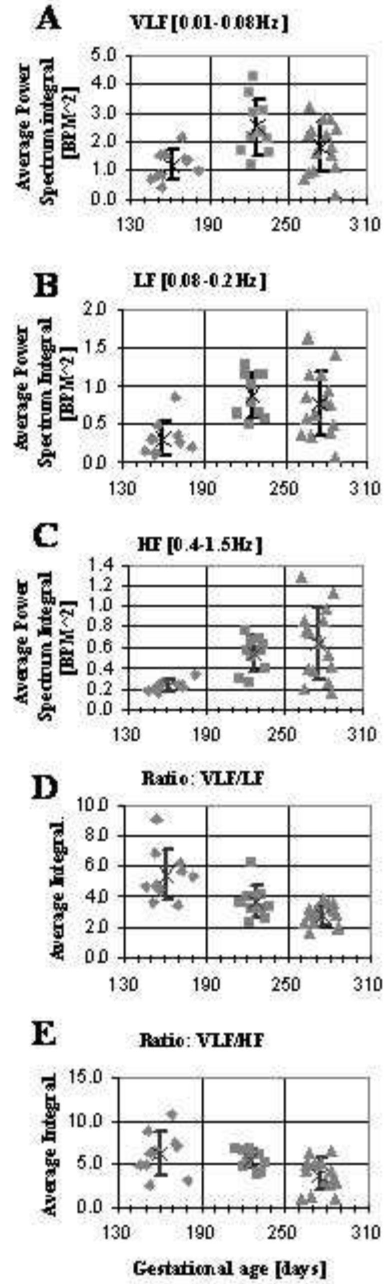

Figure 2. Changes of the power with the gestational age.

4. Discussion and conclusions

Standard spectral analysis is suitable for steady state conditions where the frequency components are not expected to vary over time. Time dependent spectrum analysis, on the other hand, allows for a more distinct understanding of the spectral components during dynamic (non-steady) or active fetal states and their change over time [8].

CWT analysis is suitable in this case because the possibility of several LF peaks (as a result of ANS instability or fetal body movements) requires a good frequency resolution in the lower frequency ranges, while in the higher frequency ranges the frequency resolution is of lesser importance. In the HF range observing whether fetal breathing motion occurred or not is of greater importance and therefore good resolution in the time domain, such as CWT provides at higher frequencies, is of greater consequence.

The power variation as a function of time is similar in the LF and VLF domains (Figure 2). In both cases the average power is greater in group 2 when compared with group 1, and the average power of group 3 is not significantly different than that of group 2. The VLF/LF ratio values of group 2, on the other hand, are significantly lower than those of group 1, i.e. the change in power in the LF domain that occurs between the middle of the second trimester (1st group) and the beginning of the third trimester (2nd group) is more pronounced when compared with the power in the VLF domain.

There might be two possibilities regarding autonomic innervation in the period between the middle of the second trimester and the beginning of the third trimester: 1) The parasympathetic activity may increase in this period of the pregnancy. 2) The frequency domain in which sympathetic activity is reflected may widen, since it is possible that an increase in the sympathetic component of the LF band occurred, along with the power increase in the VLF band.

The first possibility is strengthened by the fact that the average spectral power in the HF domain increases with gestational age (Figure 2C). It is known that in adults the vagal system is modulated by respiration at the level of cardiac vagal motor neurons [4]. Assuming that fetal respiration movements are also affected by the vagal system, one can assume that parasympathetic activity increases with gestational age.

There is no significant difference between the VLF/HF ratios of groups 1 and 2. If we assume that the HF domain has a vagal component, and the VLF domain a sympathetic one, the sympathyo-vagal average ratio does not change during the period between the middle of the second trimester, and the beginning of the third. This result indicates that both branches of the autonomous system change at the same rate during this gestational period.

As aforementioned, the average power of the 3rd group in the VLF domain is not significantly different than that of the 2nd group. This result indicates some stabilization in the sympathetic activity during the third trimester of pregnancy. This result is supported by other research that reports some neurological organization during the last trimester of pregnancy [9]. Additionally, the VLF/HF ratio in group 3 is lower than that of groups 1 and 2, a result that may indicate a decrease in the sypatho-vagal ratio towards the end of gestation.

In summary, spectral analysis techniques enable a non-invasive insight into the operational mode of the ANS. The investigation of FHR fluctuations is essential, especially when dealing with the development of the fetal ANS. The FEMO algorithm along with the CWT have proven to be sensitive tools which enable us to monitor the fetus in its natural surroundings and perform quantitative estimations of the fetal ANS.

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