Investigating Maternal-Fetal Heart Rate Coupling by High Resolution Joint Symbolic Dynamics

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Abstract

The aim of this study was to quantify short-term maternal-fetal cardiac couplings in early, mid and late gestation fetuses by using the high resolution joint symbolic dynamics (HRJSD) analysis approach. The analysis was based on fetal electrocardiograms (FECGs) of 66 healthy fetuses [22 from 16~25 weeks (GA1), 22 from 26-30 weeks (GA2) and 22 from 32-41 weeks (GA3)]. Results demonstrate that HRJSD revealed nine significant maternal–fetal coupling pattern and 4 fetal heart rate families that were able to differentiate among three gestational groups. In conclusion, the application of HRJSD revealed detailed information about short-term nonlinear maternal-fetal cardiac couplings and regulatory mechanisms (patterns) of developing autonomic nervous system function.

1. Introduction

Maternal psycho-physiological activities affect the fetal heart rate and heart rate variability. However, origins and patterns of maternal and fetal heartbeat coupling are still poorly understood. Previous studies [1] reported that FHRV changes with the physiological and psychological states of the mother, for examples, decreased FHRV with hypooxygenation of maternal arterial blood [2]; increased mean fetal heart rate with increased maternal stress and anxiety levels [3]; decreased mean fetal heart rate in synchrony with decreased mean maternal heart rate during night time [4]. This correlative and interactive behavior indicates that possible coupling between the cardiac systems of mother and fetus could be present. Van Leeuwen et al. [5] reported beat by beat phase synchronization between heartbeats of mother and fetus a marker of coupling between their autonomous cardiac systems using data driven modeling analysis and concluded that it was possible to identify the consistent influence of the heartbeat duration of maternal beats preceding the fetal beats during epochs of synchronization. However, other studies [6,7] suggested certain influence on mean fetal heart rate and heart rate variability at larger scales not beat by beat intervals. On the contrary, another study [8] failed to identify a beat-to-beat association between maternal and fetal heart rate. Ivanov et al [1] explained the reason why Van Leeuwen found the evidence of coupling while others not are because nonlinearity in synchronization of rhythms of self-sustained oscillators was considered in Van Leeuwen study. As the patterns in fetal heartbeat fluctuations change with gestation age, it can be assumed that maternal–fetal cardiac coupling may also evolve with maturation. Therefore, further investigations are needed to clarify the nature of nonlinear interaction of the maternal–fetal heart rate phase synchronization. Estimating the degree of this coupling in growing fetus could be useful in proposing novel clinical markers of healthy prenatal development and pathological deviation.

Recently high-resolution Joint Symbolic Dynamics (HRJSD) was proposed to quantify short-term cardiovascular coupling [9]. HRJSD is based on a redundancy reduction strategy and is characterized by three symbols, a threshold (individual dynamic variability, physiological) for time series transformation, and 8 coupling pattern families (resulting in 64 different coupling patterns) which quantify patterns of the autonomic regulation. We hypothesize that HRJSD indices reveal alterations of maternal and fetal cardiac coupling patterns in autonomic regulation in developing fetuses more precisely. The aim of this study is therefore to test the HRJSD method on maternal and fetal heart rate time series and look at the coupling patterns between the two systems.

2. Methods

2.1. Data

Recording of the abdominal ECG signals from 45 pregnant women at the gestational age of 16~41 weeks with normal single pregnancies were collected from Tohoku University Hospital. Three gestational age groups were considered in this study which GA1 (16-25 weeks), GA2 (26-30 weeks) and GA3 (32-40 weeks) and each of the groups has 22 subjects. All recordings (each of 1 minute's length) were sampled at 1000 Hz with 16-bit resolution. The study protocol was approved by Tohoku University Institutional Review Board and written informed consent was obtained from all subjects.

FECG traces were extracted using a method that combines cancellation of the mother's ECG signal and the blind source separation with reference (BSSR) as described in our earlier study [11]. Intervals between successive R waves of the QRS complex (i.e., R-R intervals in seconds) were calculated using the algorithm developed by Pan and Tompkins [10]. Two beat to beat intervals (BBI) time series namely fetal heart rates (fBBI) and maternal heart rates (mBBI) were created from R-R intervals of mECG and fECG signals. Both time series were visually inspected and if appropriate reedited. Afterwards these time series (fBBI, mBBI) were subsequently filtered by an adaptive filter algorithm to remove and interpolate ventricular premature beats and artefacts to obtain normal-to-normal beat time series. For the maternal-fetal coupling analyses the filtered fBBI and filtered mBBI time series were resampled (spline interpolation) using synchronization frequency fs=5Hz.

2.2. High Resolution Joint Symbolic Dynamics- HRJSD

In this study we used HRJSD [9] for quantifying the fetal-maternal heart rate couplings. Therefore, both time series (fBBI and mBBI) were transformed into symbol sequences. If X is a bivariate signal vector, x_n^{fBBI} and x_n^{mBBI} respectively.

$$X = \left[x_n^{fBBI}, x_n^{mBBI}\right]^T \quad \text{n= 0,1,2, ...} \; x \in R$$

X is then transformed into a bivariate symbol vector S which defined as

$$S = \left[S_n^{fBBI}, S_n^{mBBI}\right]^T \quad \text{n= 0,1,2, ...} \; s \in 0,1,2$$

The definitions of symbols are as follows.

$$S_n^{fBBI} = 0 \;\; when \; (x_{n+1}^{fBBI} - x_n^{fBBI}) < -l^{fBBI}$$
$$S_n^{fBBI} = 1 \;\; when \; -l^{fBBI} \leq (x_{n+1}^{fBBI} - x_n^{fBBI}) \leq l^{fBBI}$$
$$S_n^{fBBI} = 2 \;\; when \; (x_{n+1}^{fBBI} - x_n^{fBBI}) > l^{fBBI}$$

$$S_n^{mBBI} = 0 \;\; when \; (x_{n+1}^{mBBI} - x_n^{mBBI}) < -l^{mBBI}$$
$$S_n^{mBBI} = 1 \;\; when \; -l^{mBBI} \leq (x_{n+1}^{mBBI} - x_n^{mBBI}) \leq l^{mBBI}$$
$$S_n^{mBBI} = 2 \;\; when \; (x_{n+1}^{mBBI} - x_n^{mBBI}) > l^{mBBI}$$

And the threshold levels l^{fBBI} and l^{mBBI} were considered to be 0. Symbol sequences with increasing values were coded as "2", decreasing values were coded as "0" and unchanging (no variability) values were coded as "1". The symbol vector S was subdivided into short words (bin) w_k of word length k=3. Thus using three symbols led to 27 different word types for fBBI (w_{fBBI}) and mBBI (w_{mBBI}) were formed and total of number of all word type combination were 729=27x27. Then all single word types $w_{fBBI,mBBI}$ were grouped into 8 pattern families' w_f whereby the probabilities of all single word family occurrences $p(w_f)$ was normalized to 1. There were 8 pattern families ($E0$, $E1$, $E2$, $LU1$, $LD1$, $LA1$, P, V) which represent different aspects of autonomic modulation and were sorted into an 8x8 pattern family density matrix Wf resulting in 64 maternal-fetal coupling patterns. The pattern definitions are as follows.

$E0$, $E1$, $E2$: no variation within the word consisting of three symbols of type '0','1' and '2' respectively.

$LU1$, $LD1$: one variation within the word consisting of two different symbols with low increasing $LU1$ and low decreasing pattern $LD1$

$LA1$: one variation within word consisting of two different alternating symbols of type '0' and '2' with an increasing-decreasing pattern.

P and V: three variations within the word consisting of three different symbols with peak-like pattern (P) and with valley-like pattern (V).

Additionally, the sum of each (n=8) column cf_{mBBI}, the sum of each (n=8) row cf_{fBBI} and the Shannon entropy ($HRJSD_{shannon}$) of Wf were calculated from the matrix Wf as a measure of overall complexity of fetal maternal coupling.

2.3. Statistics

In this study the nonparametric Mann-Whitney U-test was performed to check the differences between GA1 vs GA2, GA2 vs GA3 and GA1 vs GA3. Significances were considered for values of p<0.01.

3. Results

Table 1. Significant HRJSD indices from maternal

fetal cardiac coupling analysis (*p<0.01) among three groups (GA1(16-25 weeks) early fetus; GA2 (26-30 weeks) and GA3 (32-41 weeks))

	U test (p values)		
Index	GA1 vs GA2	GA1 vs GA3	GA2 vs GA3
mBEI-E0/fBBI-E0	0.042	0.008*	0.211
mBEI-E0/fBBI-E2	0.107	0.050	0.862
mBEI-E0/fBBI-LU1	0.033	0.059	0.634
mBEI-E0/fBBI-LD1	0.015	0.021	0.954
mBEI-E0/fBBI-LA1	0.009*	0.000*	0.534
mBEI-E2/fBBI-E0	0.179	0.009*	0.278
mBEI-E2/fBBI-E2	0.098	0.041	0.749
mBEI-E2/fBBI-LD1	0.000*	0.018	0.044
mBEI-E2/fBBI-LA1	0.086	0.041	0.680
mBEI-LU1/fBBI-E0	0.054	0.031	0.898
mBEI-LU1/fBBI-LD1	0.194	0.010*	0.392
mBEI-LU1/fBBI-LA1	0.058	0.003*	0.451
mBEI-LD1/fBBI-E0	0.004*	0.032	0.248
mBEI-LD1/fBBI-LA1	0.013	0.002*	0.078
mBEI-LA1/fBBI-LA1	0.009	0.233	0.118
fBBI-E0	0.001*	0.000*	0.422
fBBI-E2	0.008*	0.002*	0.736
fBBI-LD1	0.001*	0.000*	0.667
fBBI-LA1	0.047	0.000*	0.177

4. Discussion

The results of HRJSD revealed that the maternal-fetal cardiac coupling slow decreasing (LD1) and alternating (LA1) short-term fetal heart rate changes in combination with slow increasing (LU1), slow decreasing (LD1) and strong maternal heart rate changes (E0) that became smaller from GA1 to GA3. On the other side strong fetal heart rate changes (E0) in combination with strong maternal heart rate increase (E0) or decrease (E2) became more pronounced in GA3.

It could be an indicator that the more matured adaptation of autonomic nervous system (ANS) to strong short-term maternal heart rate changes as an external stimuli taking place much faster at the end of the third trimester than in the beginning of the first trimester. Furthermore, it seems to be that ANS adoption of fetal heart rate changes has taken place in the first two trimesters.

Clinical observation also suggests that fetal autonomic nerves can be analyzed starting in the 17th gestational week [11]. It also suggests that parasympathetic nerves, which develop rapidly in the 18th gestational week, are not involved in the increase in Low Frequency (LF) power fetal heart variability estimated from fetal Doppler signals. Development of the sympathetic nerves begins around the 20th gestational week, later than does that of the parasympathetic nerves, and is most rapid during the 26th to 30th gestational weeks, which coincide with the period of rapid increase in the LF power [11]. Another study [12] reported that LF/HF ratio was enhanced at 32 weeks or later. Reulecke et al [13] showed a more balanced sympatho-vagal behavior of the ANS despite sympathetic activity which was revealed by decreased LF, increased HF and a trend towards lower ratio LF/HF in quiet sleep in very preterm neonates with gestational age of 26–31weeks.

In the study of Reulecke et al. [13] changes in autonomic regulation and cardiorespiratory coupling during active sleep (AS) and quiet sleep (QS) in five very preterm neonates with gestational age of 26–31weeks were investigated. They found that cardiorespiratory coupling is not yet completely developed in very preterm neonates with 26-31 weeks GA which correspond to our group GA2. In Addition, it showed that significant different regulation patterns in bivariate oscillations of heart rate and respiration during AS and QS were present. These patterns represent on the one hand a pronounced respiratory regulation in both AS and QS and on the other hand some prominent heart rate regulation patterns in QS that are independent from respiratory regulation and probably representing an increasing vagal modulation.

Measuring the degree of this coupling for developing fetuses may be useful clinical markers of healthy prenatal development and fetal cardiac anomalies. More in depth understanding of physiological underpinning of this coupling is important for future research.

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