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Analysis of maternal–fetal heart rate coupling directions with partial directed coherence

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ABSTRACT

Maternal psycho-physiological activities affect the fetal heart rate and heart rate variability. However, directions and patterns of maternal and fetal heartbeat coupling are still poorly understood. The aim of this study was to quantify the direction of short-term maternal–fetal cardiac coupling in early, mid and late gestation fetuses by using partial directed coherence (PDC) analysis approach. The analysis was based on fetal electrocardiograms (fECGs) of 66 healthy fetuses; 22 from early gestation 16–25 weeks, 22 from mid gestation 26–30 weeks and 22 from late gestation 32–41 weeks. Results of analyzing PDC demonstrated a causal influence of fetal on maternal heart rate in the early gestation, while it significantly decreased from early to mid gestation along with a significant increase of maternal to fetal coupling strength. The causal influence of maternal on fetal heart rate was the strongest in the mid gestation and remained dominant in the late gestation. In conclusion, the application of PDC revealed detailed information about short-term maternal–fetal cardiac couplings and regulatory mechanisms (patterns) of developing autonomic nervous system function.

1. Introduction

Fetal well-being during pregnancy has been widely evaluated from fluctuations of the fetal heart rate (FHR) or fetal heart rate variability (FHRV). The FHR monitoring has been used as a reliable indicator of prenatal development. However previous studies [11] reported that FHRV changes with the physiological and psychological states of the mother. Examples include decreased FHRV with hypo-oxygenation of maternal arterial blood [7]; increased mean FHR with increased maternal stress and anxiety levels [16] and decreased mean FHR in synchrony with decreased mean maternal heart rate during night time [20]. This correlative and interactive behavior indicates that a possible coupling could be present between maternal and fetal cardiac systems. In a study by Lunshof et al. a significant correlation between the fetal and maternal diurnal heart rate rhythms was found with a phase lag of −2 to +2 h [13]. The fetal suprachiasmatic nucleus, although not completely mature, is hypothesized to be involved in transferring the maternal diurnal rhythm information to the fetal heart [13]. Other studies [33,24] also suggested certain influence of maternal heart rate on mean FHR and FHRV.

In addition to the relationships in large time scales as discussed above, evidence of synchronization epochs between the heart rates at the beat-to-beat level was also reported. Van Leeuwen et al. [26] reported beat by beat phase synchronization between maternal and fetal heartbeats based on their phase locking, as a marker of coupling between their autonomous cardiac systems. It was therefore concluded that a consistent influence of the heartbeat duration of maternal beats preceding the fetal beats can be identified during epochs of synchronization. This relationship was further modeled, using the additive autoregressive processes with external contributing factors [21]. Fetal–maternal heart rate synchronization was also investigated in different settings, including controlled maternal respiration and maternal aerobic exercise [27,28]. Results of those studies suggested that high maternal breathing rate may induce the synchronization as it occurred significantly more often

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at fast maternal breathing and less at slow respiratory rates [27]. Synchronization was found less often where mothers had exercised regularly, possibly due to an increased beat-to-beat differences, higher vagal tone and slower breathing rates [28].

It was suggested that the short time fetal–maternal heart rate coupling might be via mechanical or auditory stimulation associated with the maternal rhythms, perceived by the fetus [26,21]. However, certain determination of the underlying mechanisms and patterns requires further investigation of the coupling and its directionality. It is therefore proposed in the current study to investigate the causality and strength of the relationship in each fetal–maternal direction. Moreover, 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. Further investigations are needed to clarify the nature and directionality of interaction with gestational progression. Therefore in this study the degree and directionality of the fetal–maternal heart rate coupling was estimated in growing fetuses, which could be useful in proposing novel clinical markers of healthy prenatal development and pathological deviations.

One of the most applied linear approaches in frequency domain for evaluating coupling in multivariate dynamic systems is partial directed coherence (PDC) [4]. It is based on an m-dimensional multichannel auto-regressive (MAR) model and can detect both direct and indirect causal information transfers between complex physiological signals. However the PDC method cannot be applied to the nonstationary signals and does not provide details of the coupling system dynamics. Therefore a time-variant PDC (tvPDC) approach was recently proposed by Milde et al., which provides the information about the partial correlative interaction properties applicable for short-time interactions in cardiovascular systems [15]. Following that study the normalized short time PDC (NSTPDC) was developed to evaluate dynamical changes of coupling and applied for detecting the level and direction of coupling in multivariate and complex dynamic systems [2].

We hypothesize that NSTPDC indices reveal directionality 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 NSTPDC method on maternal and fetal heart rate time series and investigate the directions of coupling between the two systems.

2. Methods

2.1. Data

Recording of the maternal and abdominal ECG signals from 66 pregnant women with normal single pregnancies were collected from Tohoku University Hospital. All cases were healthy and with the gestational age of 16–40 weeks. Three gestational age groups were considered in this study as early (16–25 weeks), mid (26–30 weeks) and late (32–40 weeks) and each of the groups had 22 subjects. The subjects in each group were independent from each other.

The abdominal ECG signals were collected using 12 electrodes: 10 on the mother's abdomen, one reference electrode on the back and one electrode at the right thoracic position. Simultaneously the Doppler ultrasound signal from 1.5 MHz Ultrasonic Transducer 5700 placed on the lower abdomen, was collected as a reference together with the abdominal ECG by a multichannel data acquisition system (fetal monitor 116, Corometrics Medical Systems Inc.). All recordings (each of 1–2 min 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 [22].

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 [19]. Two beat to beat intervals (BBI) time series namely fetal heart rates (fBBI) and maternal heart rates (mBBI) were obtained from R-R intervals of mECG and fECG signals. Both time series were visually inspected and if appropriate reedited. These time series (fBBI, mBBI) were subsequently filtered by an adaptive filter algorithm to remove and interpolate ventricular premature beats and artifacts to obtain normal-to-normal beat time series. The relative number of excluded beats (RR-intervals) was lower than 5% in relation to the relative duration of all RR intervals in the time series. For the maternal–fetal coupling analyses the filtered fBBI and mBBI time series were resampled (spline interpolation) using synchronization frequency $fs = 5$ Hz, to obtain synchronized time series (300 samples).

2.2. Heart rate variability analysis

Heart rate variability was analyzed for fetuses in different age groups. Time domain and frequency domain parameters were calculated according to HRV task force standards [1]. The complexity measures [31] such as Renyi and Shannon; symbolic dynamics [12,30] and compression entropy [6] were also analyzed for each gestational age group. The following indices from the time and frequency domains as well as nonlinear dynamics were calculated [1,31]:

- **Time domain:**

  mean FHR: mean value of NN interval time series corresponding to basic fetal heart rate (bpm).

  sdNN: standard deviation of the NN-intervals of fBBI and mBBI (ms).

  Shannon: Shannon entropy (bit) of the histogram describes the complexity of a time series and is defined on the probability distribution of kth section of the time series, whereas k is the total number of all sections. For HRV analysis the tachogram was divided in k (225) equivalent intervals with a class width of 8 ms for a range of 200–2000 ms,

  renyi2: Renyi entropy H_{renyi} (bit) is a generalization of the Shannon entropy, which describes the complexity of the time series and is defined on the probability distribution P_i of the kth section of the time series, whereas k is the total number of all sections:

$$H_{renyi}(a) = \frac{1}{1-a}\log_2 \sum_{i=1}^{k} P_i^a, \quad a > 0, a \neq 1 \tag{1}$$

  where $a = 2$ is a weighting factor for the probability distribution P_i of NN-intervals in the histogram. For HRV analysis the tachogram was divided in k equivalent intervals with a class width of 8 ms for a range of 200–2000 ms.

  renyi025: see renyi2, but with $a = 0.25$.

- **Frequency domain:**

  The fast Fourier transform was applied to estimate the power spectra equidistant linearly interpolated (10 Hz) NN interval time series. Blackman Harris window function was applied to avoid leakage effects. The following frequency domain parameters were calculated:

  VLF: very low frequency power (mBBI $\leq$ 0.04 Hz; fBBI: 0.02–0.08 Hz) (ms^2).

  LF/HF: ratio between low-frequency (mBBI: 0.04–0.15 Hz; fBBI: 0.08–0.4 Hz) power and high-frequency (mBBI: 0.15–0.4 Hz; fBBI: 0.4–1.7 Hz) power.