Investigating Foetal Heart Rate Asymmetry

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Abstract— **In this study, we have investigated how the asymmetry of beat-to-beat foetal heart rate variability (fHRV) changes during development after 35 weeks and before 32 weeks of gestation. Noninvasive foetal electrocardiogram (fECG) signals from 78 pregnant women at the gestational age from16 to 41 weeks with normal single pregnancies were analysed. Heart rate asymmetry (HRA) index that measures time asymmetry of RR interval time-series signal was used to understand the dynamics of fHRV. Results indicate that foetal HRA measured by Guzik's Index (GI) and Porta's Index (PI) changes after 35 weeks gestation compared to foetus before 32 weeks of gestation. It might be due to significant amount of maturation of the autonomic nervous system done after 35 and could potentially help identify the pathological autonomic nervous system development.**

I. Introduction

Evaluation of foetal status is important for reducing perinatal morbidity and mortality. Foetal well-being during pregnancy has been widely evaluated with fluctuations of foetal heart rate or foetal heart rate variability (fHRV) monitoring. This had started with introduction of cardiotocography (CTG – recording of foetal heart rate and force/pressure of contractions). However, initially it did not show any improvement over delivery outcomes [1] and became the main suspect for increased rate of cesarean sections [2]. In our previous studies, we have reported blind source separation with reference signals (BSSR) technique for stable and reliable extraction of fECG [3, 4].

The understanding of foetal neurological development in utero may lead to a better antenatal prediction of risk for adverse neurological outcomes, irrespective of intrapartum management. Since the foetal cardiac rhythm is controlled by the autonomic nervous system (ANS), the fHRV analysis is a simple way to understand the progressive development of ANS with gestational age (GA). At early GA, foetal heart rate is predominantly controlled by sympathetic nervous system (SNS) and arterial chemoreceptors [5]. With GA parasympathetic nervous system (PNS) matures and foetal heart rate (fHR) reduces with increasing variability [6]. In the normal foetus, interplay between SNS and PNS (ANS activity) controls the fHR and results in a difference in the beat-to-beat intervals resulting in variability of fHR tracing. This control mechanism is exerted via the cerebral cortex, the medulla oblongata, the sympathetic ganglia and the vagus nerve. The completion of the 35 gestational week marks a developmental milestone because of its association with a dramatically decreasing risk for the neonate in the case of a preterm delivery. About 90% of babies born this week can survive and lungs are almost fully developed. Initial evaluation of fHRV was primarily based on the CTG assessment guidelines [7]. However, other methods derived from adult heart rate variability were used for fHRV analysis [8-10].

Nonlinear methods of HRV analysis have become prominent, since they have improved predictive power for determination of sudden cardiac death risk and characterization of disease states associated with autonomic nervous system function [11]. Heart rate asymmetry (HRA) is a Poincaré plot based nonlinear parameter for assessing time irreversibility of heart rate or RR interval time-series signal. Asymmetry analysis can detect a more specific type of nonlinear dynamics [12] capable of producing temporal asymmetries of the heart rate and resulting in statistical properties that are different when the heart rate series are observed after time reversal. HRA is defined based on acceleration and deceleration of heart rate based on two consecutive heart rate values or RR intervals [13, 14]. In this definition, any point of Poincaré plot is classified as part of increasing or decreasing cloud with respect to line of identity (y=x). In our previous study, another definition was proposed for defining acceleration and deceleration clouds to quantify HRA based on two points of Poincaré plot [15]. Both definitions have been used with popular HRA indices namely Guzki's Index (GI), Porta's Index (PI) and Ehlers' Index (EI). HRA analysis has been reported to analyse asymmetric properties of short and long-term HRV [13, 15], altered parasympathetic nervous system activity [16], severity of obstructive sleep apnoea [17], blood pressure variability [18] and cardiovascular dynamics [19].

The aim of this study was to describe the prenatal development of integrative ANS function with gestation, exploring a new analyzing technique based on heart rate asymmetry (HRA). If recognizable patterns can be established for normal gestational development then these indices will open up diagnostic prospective.

II. Data and Methods

A. Data

Recording of the abdominal ECG signals from 78 pregnant women at the gestational age of 16~41 weeks with normal single pregnancies were collected from Tohoku

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University Hospital. Out of them 22 cases were after 35 weeks and 46 were before 32 weeks of gestational age. We kept a gap of 3 weeks of gestation age between two groups for reducing overlapping effect. Summary demography of two groups are shown in Table I. 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.

TABLE I. GROUPING OF SUBJECTS BASED ON GESTATIONAL AGE (GA).

Group	GA range (weeks)	GA (weeks) Mean ± SD
G1	20 to 32	25.89 ± 3.85
G2	35 to 41	37.95 ± 1.43

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 [4].

B. HRA and HRA Indices

HRA is defined as the imbalanced distribution of points above and below the line of identity (L_i) of the Poincaré plot (Figure 1). Points above, below and on L_i have the property $\Delta RR > 0$, $\Delta RR < 0$ and $\Delta RR = 0$ respectively, where $\Delta RR = RR_{i+1} - RR_i$ and RR_i represents the i-th RR interval.

The following HRA indices were used to measure the asymmetry of the RR interval time-series:

1) Guzik's Index (GI): Guzik et al. have defined the index for measuring the asymmetry of the time series using a Poincaré plot [13]. GI is defined as the distance of the plotted points from the line of identity. Any point on the plot is given as $P_i(RR_i, RR_{i+1})$. The distance from line of identity is calculated as:

$$D_i = \frac{|RR_i - RR_{i+1}|}{\sqrt[2]{2}} \quad (1)$$

and GI is defined as:

$$GI = \frac{\sum_{i=1}^{C(P_i^+)} (D_i^+)^2}{\sum_{i=1}^{N-1} (D_i)^2} \times 100 \quad (2)$$

where, P_i^+ represents the point above the line of identity ($RR_i < RR_{i+1}$), D_i^+ represents the corresponding distance of P_i^+ from the line of identity, $C(P_i^+)$ represents the total number of points above the line of identity and N is the total number of RR intervals.

2) *Porta's Index (PI):* In contrast to the distance from the line of identity, PI is defined based on the distribution of points below and above the line of identity. PI is calculated as the percentage of the number of points below the line of identity with respect to the total number of points [14].

$$PI = \frac{C(P_i^-)}{C(P_i^+) + C(P_i^-)} \times 100 \quad (3)$$

where, P_i^- represents the point below the line of identity ($RR_i > RR_{i+1}$), $C(P_i^-)$ and $C(P_i^+)$ represents the total number of points below and above the line of identity respectively.

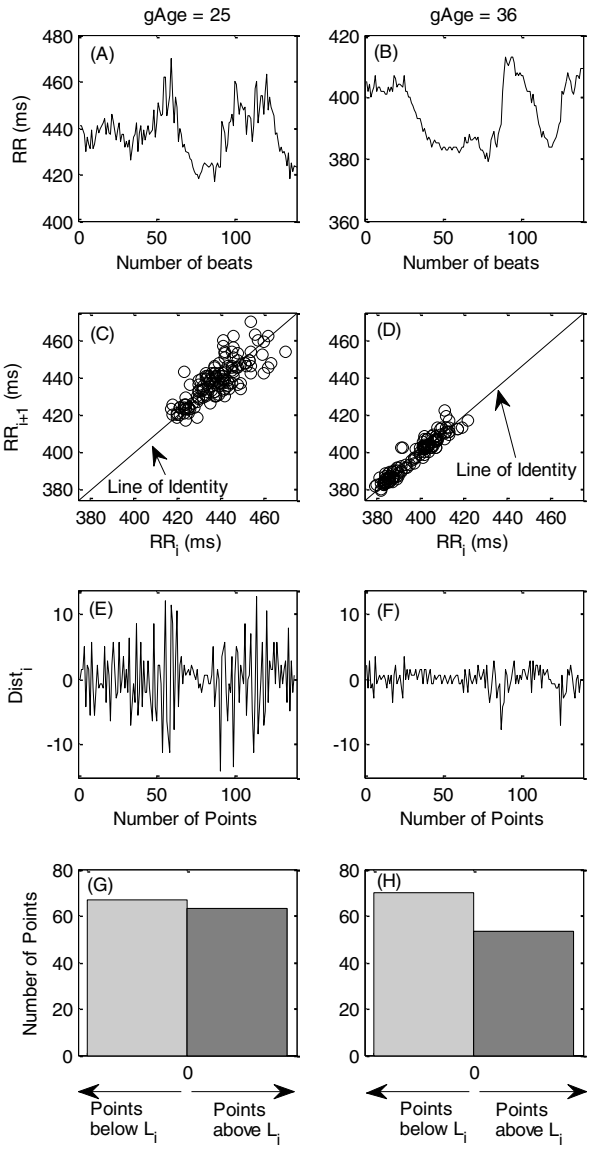

Figure 1. An example i) RR trace (A-B) of two groups; ii) corresponding $lag-1$ Poincaré plot (C-D); iii) Distance from line of identity; and iv) Distribution of points below and above line of identity.

A typical example of RR interval traces of one subject of each group is shown in Figure 2 (A-B). The lag-1 Poincaré plots corresponding to the RR intervals are shown in subplots C-D. The distance D_i of each point of the plot is shown in subplots E-F. The HRA index GI is calculated from these distances using equation 2. Subplots G-H represent the distribution of number of points above and

below line of identity corresponding to Poincaré plots of subplots C-D. This figure provides a complete visualization of how HRA indices are calculated from RR interval time series signal.

C. Statistics

The non-parametric Mann-Whitney U-test was performed to allow pair-wise testing for significant differences of HRA parameters between the two groups G1 and G2. Since, the number of subjects are small and their distribution is not normal a non-parametric test is more appropriate than parametric test. In this study, $p < 0.05$ was considered statistically significant.

III. Results

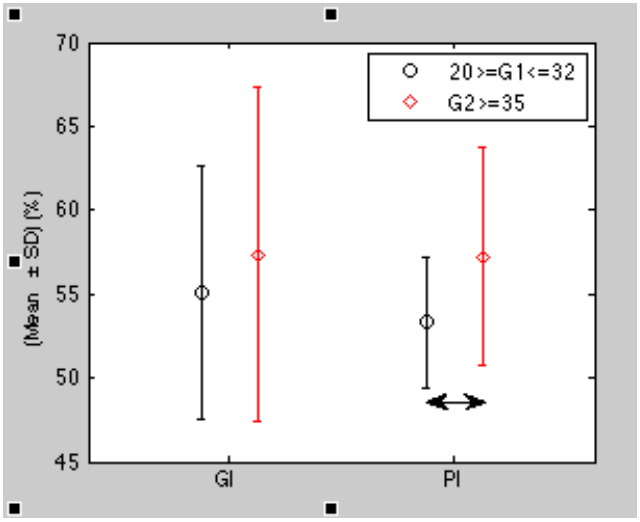

Figure 2. Mean ± SD errorbar of GI and PI of G1 and G2. Double headed arrow shows the values are statistically significantly different between G1 and G2 using Mann-Whitney U-test.

TABLE II. MEAN ± SD VALUES OF HRA PARAMETERS GI AND PI. P VALUE CALCULATED USING MANN-WHITNEY U TEST. P<0.05 IS SIGNIFICANT.

Parameter	G1 (46) Mean ± SD	G2 (22) Mean ± SD	p
GI	55.05 ± 7.54	57.37 ± 10.02	0.508
PI	53.29 ± 3.88	57.21 ± 6.49	0.006*

TABLE III. MEAN ± SD VALUES OF TIME-DOMAIN PARAMETERS. P VALUE CALCULATED USING STUDENT T-TEST. P<0.05 IS SIGNIFICANT.

Parameter	G1 (46) Mean ± SD	G2 (22) Mean ± SD	p
MeanRR (ms)	416.46 ± 28.06	409.32 ± 29.86	0.34
SDRR(ms)	13.08 ± 9.13	9.91 ± 5.70	0.14
RMSSD (ms)	6.60 ± 4.17	4.78 ± 3.86	0.09

The mean ± SD (standard deviation) values of HRA indices for each group are shown in Table II and the corresponding errorbar is depicted in Figure 2. Mean GI values were lower in early gestation age group (G1) than late gestation age group (G2). Although mean GI values were higher in G2 than G1, the difference was statistically insignificant (p>0.05). In contrast, PI values were higher in G2 than G1 and the difference was statistically significant (p<0.05).

The mean ± SD values of standard time-domain HRV parameters are shown in Table III. There are no significant differences in mean RR, $SDRR$ and $RMSSD$ values between G1 and G2 groups.

IV. Discussion

The goal of this study was to contribute to the assessment of the effectiveness of fHRV measures in further understanding the prenatal development of integrative ANS function prior to 32 and after 35 weeks of gestation, employing Poincaré plot based heart rate asymmetry analysis. Various linear and nonlinear analysis of fHRV has been applied for the classification of abnormal and compromised foetus [20, 21]. These applications are encouraged by the findings that recommendations of standard for adult HRV analysis are not directly applicable to fHRV [22, 23]. However, study of HRA in prenatal development has never been reported before to our knowledge. Poincaré plot technique can be applied on short-term data to explore the variability and dynamics in time domain as previously applied in other study [24]. Foetal electrocardiography (ECG) that provides superior measurement of beat-to-beat intervals was used in this study.

There are various measures available to quantify asymmetry in cardiovascular signals. Recent studies suggest that simple HRA indices such as Guzik's and Porta's index are sensitive to shifts in sympatho-vagal balance. PI compares the number of increments and decrements in the RR time-series signal (i.e. deceleration and acceleration of the heart rate), whereas GI compares the magnitude of such acceleration and deceleration. These different methods may provide partially independent information and their simultaneous quantification might be useful in order to detect asymmetry more comprehensively.

Within the context of foetal development with gestational age the current results highlight that the asymmetry of the number of accelerations and decelerations (measured by PI), that is, sympathetic and parasympathetic influence changed significantly at late GA. However, the asymmetry of the magnitude of these accelerations/decelerations (measured by GI) remained similar in both groups. Therefore, the results showed that there is a significant variation in number of acceleration and deceleration of RR intervals with gestation age rather than magnitude of such acceleration or deceleration.

PI values greater than 50% indicates that there are higher number HR acceleration points (point below line of identity using RR intervals) than deceleration. Therefore, higher values of PI in G2 (gestation age greater than 35) suggest that there are more numbers of instant heart rate increments in this group than G1. Since increase in HR is linked with increased sympathetic activity, the increased value of PI in G2 may signify the maturation of sympathetic nervous system.

V. Conclusion

In summary, HRA indices of fHRV can be used to identify a foetus as early (before 32 weeks) or late (after 35 weeks), which takes into consideration the influence an individual beat has on subsequent beats in the time series. Increasing *PI* of late foetus group is an alternate expression of increased sympathetic activity. Foetal development causes an alteration in the HRA indices that correlates with the progressive innervations of sympathetic activity towards delivery. However, further study with longer recording time and increased number of subjects is necessary to support the reported findings.

References

[1] Z. Alfirevic, D. Devane, and G. M. L. Gyte, "Continuous cardiotocography (CTG) as a form of electronic fetal monitoring (EFM) for fetal assessment during labour," *Cochrane Database of Systematic Reviews*, no. 3, 2006.

[2] P. J. Steer, "Has electronic fetal heart rate monitoring made a difference?," *Seminars in Fetal & Neonatal Medicine,* vol. 13, no. 1, pp. 2-7, Feb, 2008.

[3] S. Furukawa, H. Sameshima, L. Yang *et al.*, "Acetylcholine Receptor Agonist Reduces Brain Damage Induced by Hypoxia-Ischemia in Newborn Rats," *Reproductive Sciences,* vol. 18, no. 2, pp. 172-179, Feb, 2011.

[4] M. Sato, Y. Kimura, S. Chida *et al.*, "A novel extraction method of fetal electrocardiogram from the composite abdominal signal," *Ieee Transactions on Biomedical Engineering,* vol. 54, no. 1, pp. 49-58, Jan, 2007.

[5] P. Renou, W. Newman, and C. Wood, "Autonomic Control of Fetal Heart Rate," *American Journal of Obstetrics and Gynecology,* vol. 105, no. 6, pp. 949-&, 1969.

[6] R. Gagnon, K. Campbell, C. Hunse *et al.*, "Patterns of Human-Fetal Heart-Rate Accelerations from 26 Weeks to Term," *American Journal of Obstetrics and Gynecology,* vol. 157, no. 3, pp. 743-748, Sep, 1987.

[7] FIGO, "Guidelines for the use of fetal monitoring," *Int J Gynaecol Obstet,* vol. 25, pp. 159-167, 1986.

[8] S. M. Pincus, and R. R. Viscarello, "Approximate Entropy - a Regularity Measure for Fetal Heart-Rate Analysis," *Obstetrics and Gynecology,* vol. 79, no. 2, pp. 249-255, Feb, 1992.

[9] D. G. Chaffin, C. C. Goldberg, and K. L. Reed, "The Dimension of Chaos in the Fetal Heart-Rate," *American Journal of Obstetrics and Gynecology,* vol. 165, no. 5, pp. 1425-1429, Nov, 1991.

[10] N. A. J. Gough, "Fractal Analysis of Fetal Heart-Rate-Variability," *Physiological Measurement,* vol. 14, no. 3, pp. 309-315, Aug, 1993.

[11] A. Voss, J. Kurths, H. J. Kleiner *et al.*, "The application of methods of non-linear dynamics for the improved and predictive recognition of patients threatened by sudden cardiac death," *Cardiovascular Research,* vol. 31, no. 3, pp. 419-433, Mar, 1996.

[12] G. Weiss, "Time-Reversibility of Linear Stochastic-Processes," *Journal of Applied Probability,* vol. 12, no. 4, pp. 831-836, 1975.

[13] P. Guzik, J. Piskorski, T. Krauze *et al.*, "Heart rate asymmetry by Poincaré plots of RR intervals," *Biomed Tech (Berl),* vol. 51, no. 4, pp. 272-5, Oct, 2006.

[14] A. Porta, K. R. Casali, A. G. Casali *et al.*, "Temporal asymmetries of short-term heart period variability are linked to autonomic regulation," *American Journal of Physiology-Regulatory Integrative and Comparative Physiology,* vol. 295, no. 2, pp. R550-R557, Aug 1, 2008.

[15] C. Karmakar, A. Khandoker, J. Gubbi *et al.*, "Defining asymmetry in heart rate variability signals using a Poincaré plot," *Physiological Measurement,* vol. 30, no. 11, pp. 1227-1240, 2009.

[16] C. Karmakar, A. Khandoker, and M. Palaniswami, "Investigating the changes in heart rate asymmetry (HRA) with perturbation of parasympathetic nervous system," *Australas Phys Eng Sci Med.,* vol. 35, no. 4, pp. 465-474, 2012.

[17] P. Guzik, J. Piskorski, K. Awan *et al.*, "Obstructive sleep apnea and heart rate asymmetry microstructure during sleep," *Clin Auton Res,* vol. 23, no. 2, pp. 91-100, Apr, 2013.

[18] P. Guzik, J. Piskorski, T. Krauze *et al.*, "Asymmetric features of short-term blood pressure variability," *Hypertens Res,* vol. 33, no. 11, pp. 1199-205, Nov, 2010.

[19] P. Guzik, J. Piskorski, T. Krauze *et al.*, "Partitioning total heart rate variability," *Int J Cardiol,* vol. 144, no. 1, pp. 138-9, Sep 24, 2010.

[20] J. Gieraltowski, D. Hoyer, F. Tetschke *et al.*, "Development of multiscale complexity and multifractality of fetal heart rate variability," *Autonomic Neuroscience-Basic & Clinical,* vol. 178, no. 1-2, pp. 29-36, Nov, 2013.

[21] P. Van Leeuwen, D. Cysarz, F. Edelhauser *et al.*, "Heart rate variability in the individual fetus," *Autonomic Neuroscience-Basic & Clinical,* vol. 178, no. 1-2, pp. 24-28, Nov, 2013.

[22] U. Schneider, B. Frank, A. Fiedler *et al.*, "Human fetal heart rate variability-characteristics of autonomic regulation in the third trimester of gestation," *Journal of Perinatal Medicine,* vol. 36, no. 5, pp. 433-441, 2008.

[23] S. Lange, P. Van Leeuwen, D. Geue *et al.*, "Influence of gestational age, heart rate, gender and time of day on fetal heart rate variability," *Medical & Biological Engineering & Computing,* vol. 43, no. 4, pp. 481-486, Jul, 2005.

[24] H. F. Sandmire, and R. K. DeMott, "Electronic fetal heart rate monitoring: research guidelines for interpretation," *Am J Obstet Gynecol,* vol. 179, no. 1, pp. 276-7, Jul, 1998.