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Author/s:

Karmakar, C;Kimura, Y;Palaniswami, M;Khandoker, A

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Analysis of Fetal Heart Rate Asymmetry before and after 35 weeks of gestation

Chandan Karmakar^{1,2*}, Yoshitaka Kimura³, Marimuthu Palaniswami¹

and Ahsan Khandoker^{1,4}

¹ Department of Electrical & Electronic Engineering, University of Melbourne, Melbourne, Australia

² Centre for Pattern Recognition and Data Analytics, Deakin University, Geelong, Australia

³ Graduate School of Medicine, Tohoku University, Sendai, Japan

⁴ Department of Biomedical Engineering, Khalifa University of Science, Technology and Research, Abu Dhabi, UAE

Email: karmakar@unimelb.edu.au; ykimura@med.tohoku.ac.jp; palani@unimelb.edu.au;
ahsank@unimelb.edu.au;

Address of corresponding author

Department of Electrical & Electronic Engineering
University of Melbourne
Parkville, VIC 3010
Melbourne, Australia
Email: karmakar@unimelb.edu.au
Phone: +61-3-90357614

Abstract— In this study, we have investigated the evidence of fetal heart rate asymmetry and how the fetal heart rate asymmetry changes before and after 35 weeks of gestation. Noninvasive fetal electrocardiogram (fECG) signals from 45 pregnant women at the gestational age from 16 to 41 weeks with normal single pregnancies were analysed. A nonlinear parameter called heart rate asymmetry (HRA) index that measures time asymmetry of RR interval time-series signal was used to understand the changes of HRA in early and late fetus groups. Results indicate that fetal HRA measured by Porta's Index (PI) consistently increases after 35 weeks gestation compared to foetus before 32 weeks of gestation. It might be due to significant changes of sympatho-vagal balance towards delivery with more sympathetic surge. On the other hand, Guzik's Index (GI) showed a mixed effect i.e., increases at lower lags and decreases at higher lags. Finally, fHRA could potentially help identify normal and the pathological autonomic nervous system development.

1. Introduction

Evaluation of fetal status is important for reducing perinatal morbidity and mortality. Advancements of science and technology promises to elucidate information regarding developmental changes during antenatal period. Thus, fetal death remains a potentially preventable condition that has major personal, social and financial implications for both families and the broader community.

Fetal well-being during pregnancy has been widely evaluated with fluctuations of fetal heart rate or fetal heart rate variability (fHRV) monitoring. This had started with introduction of cardiotocography (CTG – recording of fetal 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]. After introducing the CTG interpretation guidelines in order to lower the number of neonates with asphyxia and cesarean sections [3, 4], it remains the most prevalent method for fetal surveillance [5, 6]. Besides poor standard of interpretation and high intra/inter observer variability [2], CTG delivers only the momentary heart rate with limited accuracy [7]. Therefore, CTG derived fetal heart rate time-series is not suitable for beat-to-beat analysis, which is clinically more significant than long-term measure [8, 9]. Fetal magnetocardiogram (fMCG) overcomes these limitations of CTG and provides a non-invasive approach for monitoring fetal cardiac activity with sufficient precision [10, 11]. However, fMCG requires magnetically shielded rooms (MSR), which limits the regular use of the device due to the

high cost of MSR materials. Like fMCG, fetal electrocardiogram (fECG) is a non-invasive method for monitoring beat-beat fetal cardiac activity with sufficient precision. Although, extraction of fECG is difficult, we have reported blind source separation with reference signals (BSSR) technique for stable and reliable extraction of fECG [12-15]. Therefore, fECG is the simple and convenient method for non-invasive monitoring of fetal cardiac activity.

The understanding of fetal neurological development in utero may lead to a better antenatal prediction of risk for adverse neurological outcomes, irrespective of intrapartum management. Since the fetal 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, fetal heart rate is predominantly controlled by sympathetic nervous system (SNS) and arterial chemoreceptors [16]. With GA parasympathetic nervous system (PNS) matures and fetal heart rate (fHR) reduces with increasing variability [17]. In the normal fetus, 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 [3]. However, other methods derived from adult heart rate variability were used for fHRV analysis [18-21]. Since recent studies [22-25] have demonstrated that the recommendation standards for adult heart rate variability analysis [26] cannot be directly applied to fHRV studies, new linear and nonlinear parameters are started to be tested to analyze growth of fetus, classifying abnormal fHR and fetal status etc. [27-36]. Mostly used nonlinear methods are fractal dimension [18, 19, 27] and entropy based regularity measurements (approximate entropy and sample entropy) [20, 28, 29, 31]. Recently we have used complex correlation measure (CCM), which measures the variability in the temporal structure of Poincaré, along with standard descriptors (SD1 and SD2) to investigate the changes in dynamics and variability of fHRV time-series with GA [37].

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 [38]. 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 [39] 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 rates or RR intervals [40, 41]. 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 [42]. 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 [40, 42], altered parasympathetic nervous system activity [43], severity of apnea [44], blood pressure variability [45] and cardiovascular dynamics [46]. There is no study done to look at HRA in fetal heart rates.

Therefore, the aim of this study was to check whether HRA is present in fetal heart rates and then how HRA changes over the gestational progression.

2. Data and Methods

2.1 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 University Hospital. To evaluate change of HRA with gestational age, we divided the fetuses into two groups G1 ($\in [20,32]$) and G2 ($\in [35,41]$). Since development of sympathetic nervous system completes by 35 weeks of gestation [15, 47], which is also associated with a dramatically decreased risk for the neonate in the case of a preterm delivery, it was used to divide the fetuses into two groups. We kept a gap of 3 weeks of gestation age between two groups for reducing overlapping effect. Out of 28 fetuses 22 cases were after 35 weeks and 46 were before 32 weeks of gestational age. Summary demography of two groups are shown in Table 1.

Table 1: Grouping of subjects based on gestational age (GA)

| Group | GA range (weeks) | GA (weeks) Mean \pm SD |
|-------|------------------|--------------------------|
| G1 | 20 to 32 | 25.89 \pm 3.85 |
| G2 | 35 to 41 | 37.95 \pm 1.43 |

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 [15]. 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 [48]. Once RR intervals were calculated, the ectopic beat was selected automatically based on a predefined heart rate range. For any RR interval, if the instantaneous heart rate is lesser than 100 beats/minute or higher than 240 beats/minute then the interval was marked as ectopic and removed from the RR interval time-series. After artifact removal the average length of RR interval time-series for 68 recordings was 142 beats.

2.2 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.

2.2.1 Guzik's Index (GI):

Guzik et al. have defined the index for measuring the asymmetry of the time series using a Poincaré plot [40]. 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:

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

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 a 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.

2.2.2 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 [41].

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

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

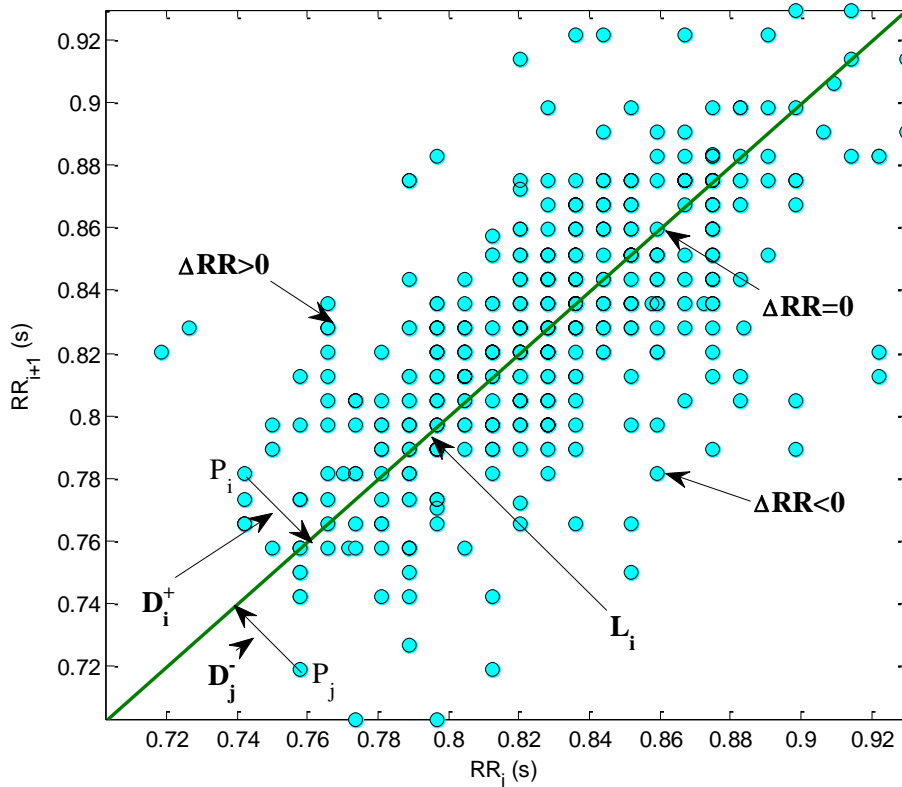


Figure 1: Properties of points in a lag-1 Poincaré plot used to calculate Guzik's and Porta's asymmetry indexes.

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

2.3 Multi-lag HRA

Poincaré plot is a time-delayed map of time-series signal, where the time delay termed as lag of the plot. Therefore, lag is an inherent property of Poincaré plot. The conventional method of quantifying HRA uses successive RR intervals with the implicit assumption that the current beat is influenced by the immediately preceding beat. However, the delay of such influence is affected by the variation of baroreflex sensitivity and therefore can be greater than one beat [49, 50]. For example, the baroreflex sensitivity is reduced in chronic renal failure (CRF)

patients [51], which augments the delay in the heart rate response. **Therefore, a heartbeat influences not only the beat immediately following it, but also up to 6–10 beats downstream [52] and several researchers confirmed that the lag is associated with disease processes [53, 54].** Thus, successive RR interval duplets will likely underestimate the role of the autocovariance function of RR intervals i.e., the ability of heart beats to influence a train of succeeding beats. Moreover, the autocovariance function of RR intervals captures additional aspects of HRV (e.g. non-linearity) that are otherwise masked by the strong correlation between successive beats if lag 1 (n vs $n + 1$ beats) HRA is used. Therefore, we hypothesized that multi-lag HRA analysis will provide better understanding about the development of ANS in foetus with gestation.

For multi-lag HRA analysis, we have introduced the lag (m) in equation (2) and (3), used to calculate GI and PI from RR interval time series signal. In $lag - m$ Poincaré plot the i -th point on the plot is the duplet $P_i^m(RR_i, RR_{i+m})$. Hence, in the multi-lag HRA analysis GI and PI indices were calculated using following equations:

$$GI_m = \frac{\sum_{i=1}^{C(P_i^{m+})} (D_i^{m+})^2}{\sum_{i=1}^{N-1} (D_i^m)^2} \times 100 \quad (4)$$

$$PI = \frac{C(P_i^{m-})}{C(P_i^{m+}) + C(P_i^{m-})} \times 100 \quad (5)$$

where, P_i^{m+} and P_i^{m-} represent the point above and below line of identity at lag m . $C(P_i^{m+})$ and $C(P_i^{m-})$ represent the number of points below and above line of identity at lag m . D_i^m represents the distance of point P_i^m from line of identity. In this study, we have used lag $m = 1$ to 8 for analyzing HRA of fetal RR interval time-series signal.

2.4 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 is small and their distribution is not normal, **which was tested using Lilliefors test**, a non-parametric test is more appropriate than parametric test.

For each group, we estimated the dependence of the HRA indices on fetal maturation by calculating their correlation with GA. The Spearman's rank-order correlation coefficient r was calculated to measure the strength of the association between HRA index and gestation age. Spearman's rank correlation coefficient is a nonparametric (distribution-free) rank statistic, which measures the monotone association that is used when the distribution of data

makes Pearson's correlation coefficient undesirable or misleading. It assesses how well an arbitrary monotonic function can describe the relationship between two variables, without making any assumptions about the frequency distribution of the variables. Besides strength of the correlation it also provides significance of the correlation measured as p . In this study, $p < 0.05$ was considered statistically significant.

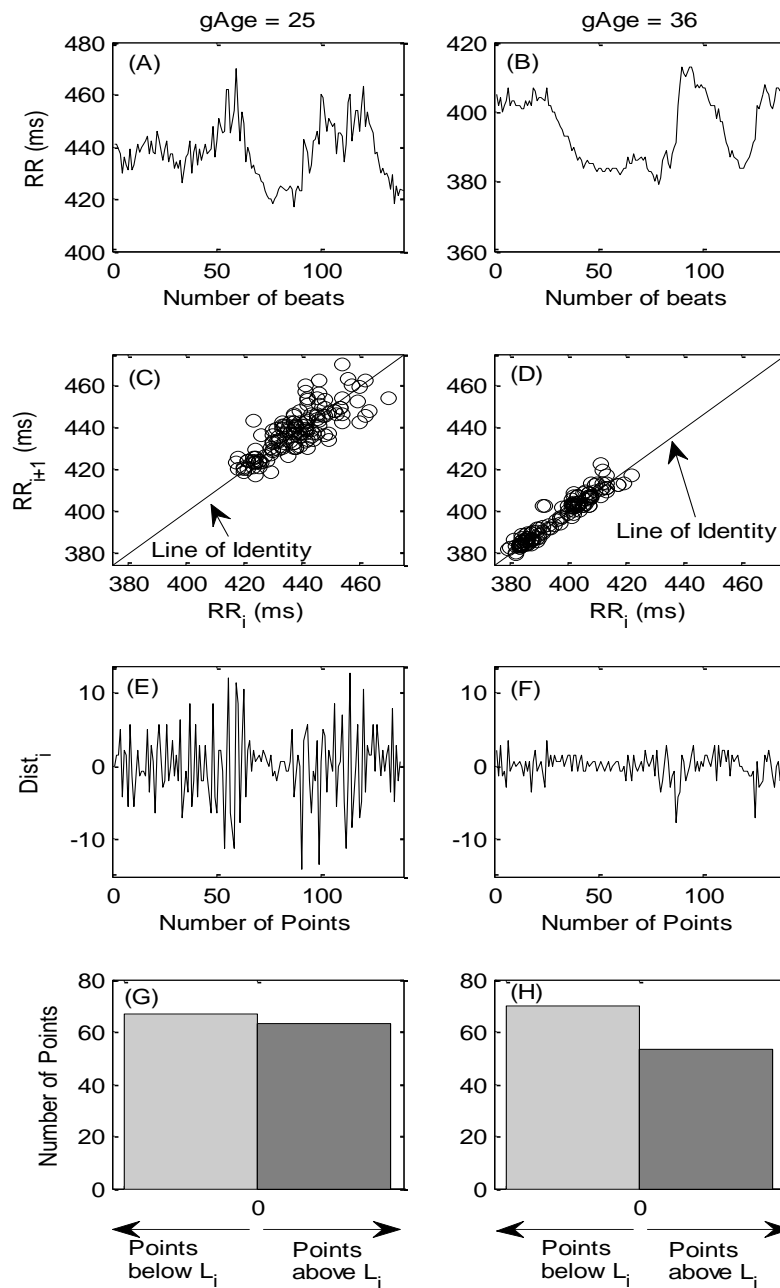


Figure 2: An example i) RR trace (A-B) of two groups; ii) corresponding lag – 1 Poincaré plot (C-D); iii) Distance from line of identity; and iv) Distribution of points below and above line of identity.

3. Results

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 represents the distribution of number of points above and below line of identity corresponding to Poincaré plots of subplots C-D. Figure 2 provides a complete visualization of how HRA indices are calculated from RR interval time series signal.

The mean \pm SD (standard deviation) values of HRA indices for each group are shown in Table 2 and the corresponding error bar plot is shown in Figure 3. Mean GI values were higher in early gestation age group (G1) than late gestation age group (G2) at all lags $m=1$ to 8. Although mean GI values were higher in G1 than G2 at all lags, the difference was statistically **not significant** ($p>0.05$). In contrast, PI values were higher in G2 than G1 at all lags and the difference was statistically significant ($p<0.05$) for lags $m=1$ to 4.

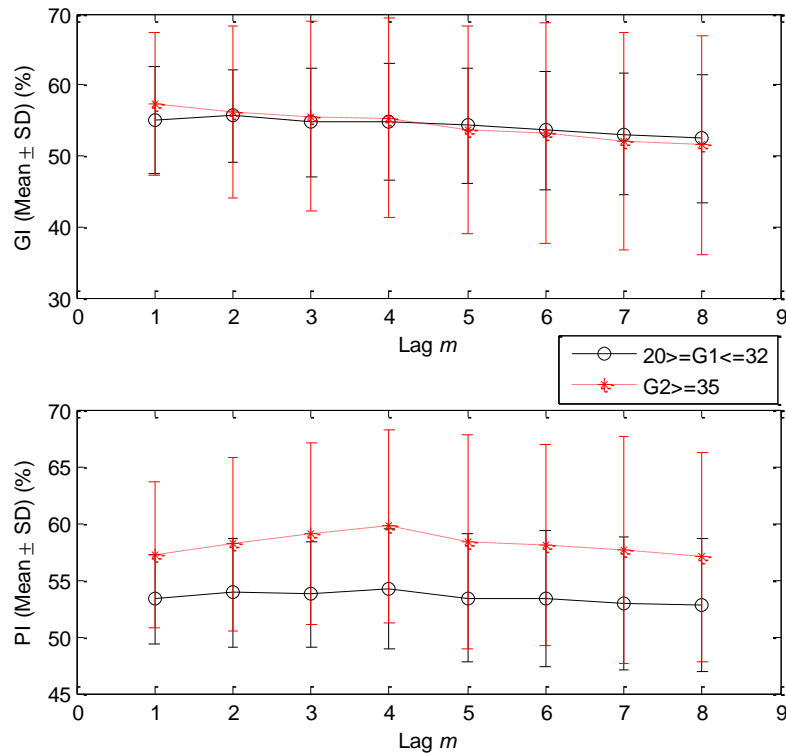


Figure 3: Errorbar (Mean \pm SD) of HRA indices GI and PI at lags $m=1\sim 8$.

Table 2. Mean \pm SD values of HRA parameters (GI and PI) at lags $m=1\sim 8$. p values were calculated using Mann-Whitney U test. * indicates values between two groups is significant ($p<0.05$).

| Parameter | Lag m | G1 Mean \pm SD | G2 Mean \pm SD | p |
|-----------|-------|------------------|-------------------|--------|
| GI | 1 | 55.05 \pm 7.54 | 57.37 \pm 10.02 | 0.508 |
| | 2 | 55.60 \pm 6.49 | 56.17 \pm 12.16 | 0.516 |
| | 3 | 54.70 \pm 7.68 | 55.54 \pm 13.41 | 0.335 |
| | 4 | 54.76 \pm 8.16 | 55.32 \pm 14.06 | 0.246 |
| | 5 | 54.24 \pm 8.05 | 53.59 \pm 14.63 | 0.420 |
| | 6 | 53.58 \pm 8.38 | 53.18 \pm 15.46 | 0.362 |
| | 7 | 53.04 \pm 8.57 | 52.10 \pm 15.31 | 0.459 |
| | 8 | 52.44 \pm 8.98 | 51.57 \pm 15.43 | 0.467 |
| PI | 1 | 53.29 \pm 3.88 | 57.21 \pm 6.49 | 0.006* |
| | 2 | 53.86 \pm 4.75 | 58.15 \pm 7.65 | 0.014* |
| | 3 | 53.72 \pm 4.58 | 59.07 \pm 8.06 | 0.008* |
| | 4 | 54.24 \pm 5.32 | 59.71 \pm 8.56 | 0.009* |
| | 5 | 53.39 \pm 5.63 | 58.39 \pm 9.45 | 0.060 |
| | 6 | 53.36 \pm 5.93 | 58.08 \pm 8.89 | 0.064 |
| | 7 | 52.92 \pm 5.83 | 57.62 \pm 10.02 | 0.111 |
| | 8 | 52.76 \pm 5.86 | 57.01 \pm 9.17 | 0.114 |

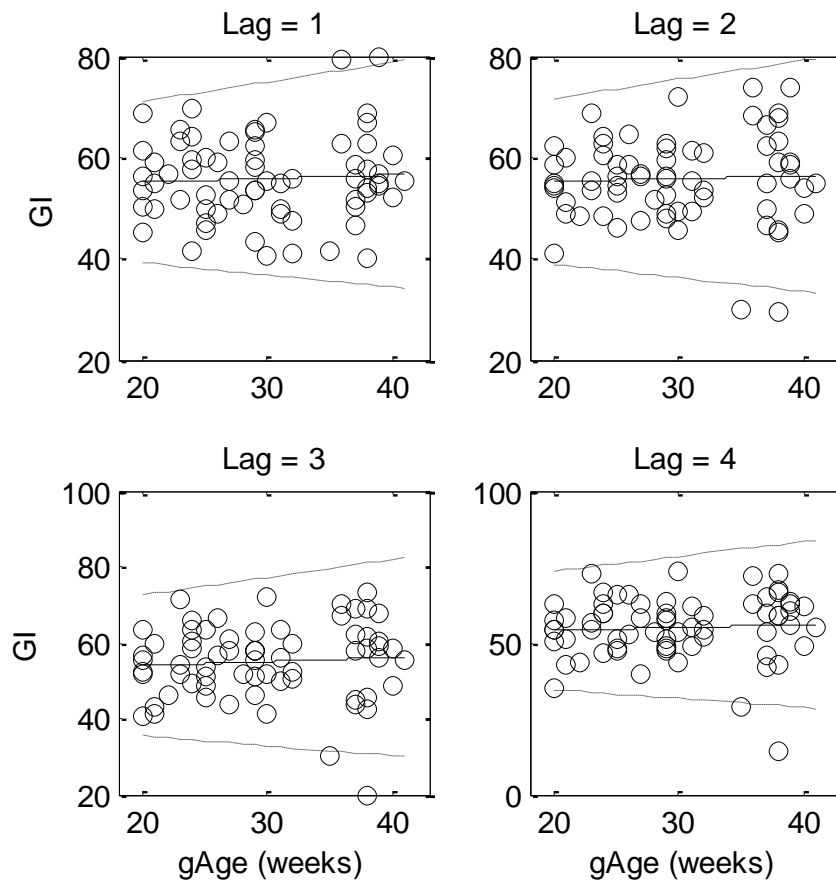


Figure 4: Correlation between GI and gestational age at lags $m=1\sim 4$.

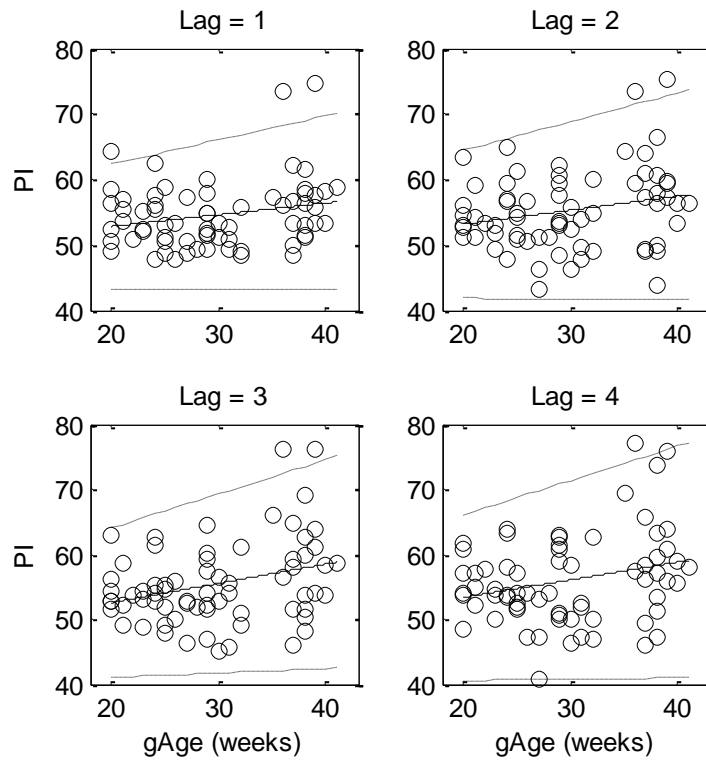


Figure 5: Correlation between PI and gestational age at lags $m=1\sim 4$.

Table 3: Spearman correlation coefficient (R) and corresponding p values for all lags.

| Parameter | Lag m | R | P |
|-----------|---------|------|------|
| GI | 1 | 0.06 | 0.65 |
| | 2 | 0.04 | 0.75 |
| | 3 | 0.07 | 0.57 |
| | 4 | 0.06 | 0.61 |
| | 5 | 0.00 | 0.99 |
| | 6 | 0.04 | 0.77 |
| | 7 | 0.04 | 0.77 |
| | 8 | 0.04 | 0.72 |
| PI | 1 | 0.23 | 0.06 |
| | 2 | 0.23 | 0.06 |
| | 3 | 0.30 | 0.01 |
| | 4 | 0.26 | 0.03 |
| | 5 | 0.22 | 0.07 |
| | 6 | 0.23 | 0.06 |
| | 7 | 0.24 | 0.05 |
| | 8 | 0.22 | 0.07 |

The relationships of *GI* and *PI* at multiple lags (1~4) with gestational ages are illustrated in Figures 4 and 5. *GI* was increasing with gestational ages however the relationships were statistically **not significant** ($p > 0.05$ in

Table 3). Similar to GI, PI was also increasing with gestational ages and significant ($p < 0.05$) correlations were only seen at lags 3 and 4 (Table 3).

4. 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 have been applied for the classification of abnormal and compromised foetus [55, 56]. These applications are encouraged by the findings that recommendations of standard for adult HRV analysis are not directly applicable to fHRV [22-25]. 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 studies [4, 14]. Fetal electrocardiography (ECG) that provides superior measurement of beat-to-beat intervals was used in this study. For many of the current HRV analysis methods the assumption is that for all consecutive beats, each beat only has influence on the subsequent beat, whereas it has been shown that each beat in a time series can have an influence on up to ten beats downstream [52]. This opened up the avenue for analyzing multi-lag HRA characteristics of beat to beat fetal heart rate time series and its usefulness in clinical application.

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 fetal 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 for lags $m=1$ to 4. However, the asymmetry of the magnitude of these accelerations/decelerations (measured by GI) remained similar in both groups for all lags. 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% indicate 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. This findings is supported by a histologic study of the cardiac conduction system in human fetal hearts, which reported that the sinus node is completely developed by the 6th gestational week, the atrioventricular node by the 10th gestational week, and the entire functional conduction system by the 16th gestational week [57]. However, 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 low frequency (LF) power [47].

The mean PI values of late foetus group were initially increased for lags $m=1$ to 4 and then decreased with increasing lags $m=5$ to 8. This indicates that the sympathetic influence increases with increasing lags up to 4 and then decreases with further increasing in lag. On the other hand, in early foetus group mean PI consistently decreased with increasing lags $m=1$ or 8, which could mean that parasympathetic influence of current beat increases with increasing lag (distant heart beats) in early foetus group.

Both GI and PI showed positive correlation with gestation age, which indicates that maturation of autonomic nervous system increases fetal heart rate asymmetry. In contrast to PI, which showed significant correlation at lag 3 and 4, GI showed no significant correlation with gestation age. This indicates that the effect of gestation age is more pronounced in the asymmetries of number of acceleration/deceleration rather than magnitude. Moreover, such relationship is strongly pronounced at lag 3 and 4 than lag 1. Therefore, multi-lag analysis is required to better understand the fetal autonomic nervous system development with gestation using heart rate asymmetry analysis.

This study is limited by the small number of subjects and short length recordings. Although no study has been reported result of HRA on 1 minute ECG recordings, it has been applied on short-term analysis of 5 minute ECG recordings of healthy adult subjects [40, 42]. Therefore, further study is required on large cohort with longer recordings to confirm the repeatability of the findings of the present study.

5. Conclusion

In summary, a HRA index (Porta's Indices) of fHRV at multiple lags increases from early (before 32 weeks) to late (after 35 weeks). Increasing PI of late foetus group could be an alternate expression of shifted sympatho-vagal balance to an increased sympathetic activity. Fetal development causes an alteration in the HRA indices that correlates with the progressive innervations of sympathetic activity towards delivery.

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