Analysis of heart rate variation and foetal quiet sleep cycle correlation for normal and suspicious foetuses

Guangfei Li, Song Zhang, Lin Yang, Shufang Li, Yan Wang, Yangyu Zhao, Yimin Yang, Dongmei Hao, Xuwen Li, Lei Zhang and Mingzhou Xu

College of Life Science and Bio-engineering, Beijing University of Technology, Beijing, PR China; Obstetrics and Gynecology, Peking University Third Hospital, Beijing, PR China; Beijing Yes Medical Devices Co., Ltd., Beijing, PR China; Beijing Aerospace Changfeng Co., Ltd., Beijing, PR China

ABSTRACT
Cardiotocography (CTG) is the basic method of monitoring foetal condition in the perinatal period. However, due to the limited insight into the CTG generation mechanism, some CTG recordings can be mistreated as a predictor of neonatal asphyxia, leading to a wrong assessment of the foetal status and improper obstetric intervention. Therefore, in case of suspicious CTG indications, a reliable verification of the true foetal status is vital for reducing the clinical diagnosis false-positive rate and avoiding the unnecessary obstetrician intervention. The paper presents the results obtained for 44 foetuses on the shares of three heart rate variation (HRV) ranges and quiet sleep cycles. This approach uses the parameters of the HRV range shares and quiet sleep cycles to analyse different types of foetuses. The results obtained show that most parameters reveal significant differences between normal and suspicious groups. This is quite lucrative for defining a set of coefficients, whose incorporation into a classifier will improve the accuracy of distinguishing the normal foetuses from suspicious ones.

KEYWORDS
Foetal heart rate; foetal quiet sleep; HRV range share

Introduction

The conventional cardiotocography (CTG), which utilises the recording of foetal heartbeat and the uterine contractions during pregnancy, is the most widely used method for foetal surveillance. However, its visual interpretation is somewhat subjective and possesses certain intra- and inter-observer differences [1]. This challenge has been addressed by multiple researchers who tried to improve the accuracy of the evaluation of cardiotocographic recordings and reduce the variations of their interpretation [2]. The recording method of foetal heart rate (FHR) signal is usually non-invasive, using the ultrasound Doppler method, whereas the sensor is placed on the pregnant woman’s abdomen. In the intrapartum period, the internal monitoring can be also applied by placing a sensor on the foetal scalp [3].

The foetal baseline variation is the result of the interaction between excited sympathetic and vagus nerves, the former increasing and the latter decreasing the heart rate. The foetal baseline variation cases include the variation loss, small variation, normal variation, and significant variation, while the beat–beat variability can be short- or long-term one. The foetal baseline falling within a certain range implies that foetal central nervous system, plant nerve regulation and heart function are perfect, and, thus, the foetus has a certain reserve capacity. In the state of the perinatal medicine, the FHR variation interpretation is the basic diagnostic tool, which is applied to the antepartum assessment of foetal well-being [4].

In this study, the foetal electrocardiography (FECG) monitor is used to acquire the FHR signals of length exceeding 10 h. Then the heart rate variation (HRV) value is split into three (short, medium and high) ranges, and their share is used in the proposed approach to analyse the FHR signals obtained from FECG recordings for normal foetuses and those with suspicious CTG indications (hereinafter referred to as suspicious foetuses). This approach combines different groups of indices including the mean value of baseline, the share of HRV range shares and quiet sleep cycles to analyse different types of foetuses. The results obtained show that most parameters reveal significant differences between normal and suspicious groups. This is quite lucrative for defining a set of coefficients, whose incorporation into a classifier will improve the accuracy of distinguishing the normal foetuses from suspicious ones.

Subjects and methods

Subjects

Forty-four FECG recordings were recruited for the study, with pregnant women’s age of 31.4 ± 3.7 years, and
gestational age (GA) of 38.0 ± 2.4 weeks. All the study participants had a singleton foetus and no reported prior experience of adverse outcomes. This research was approved by the Peking University Third Hospital Ethics Committee and the participants gave signed informed consent before their enrolment.

**Signal acquisition**

An FECG monitor (Monica AN24 by Monica Healthcare Inc., USA) was used to record mothers’ heart rate and FHR signals, while only those corresponding to the antepartum period were analysed in this study. The average duration of 44 recordings under study is 17.3 ± 4.9 h, while the share of lost tracks in each subject recordings was lower than 30%.

All subjects were subjected to the non-stress test (NST), which implies that the foetus does not take stress during the test. The main objective of NST is to measure FHR in response to foetal heart movements. A healthy foetus will increase its heart rate during movement, and decrease its heart rate at rest. NST involves attaching one sensor belt to the mother’s abdomen to acquire FHR and another sensor belt to acquire uterine contractions. The test continues 20 or 40 min. If there is no movement during NST, it does not necessarily indicate the foetus has a problem, since the foetus may be asleep.

According to the baseline heart rate and HRV, the NST cases can be classified as reactive, suspicious and no response cases. In this study, 21 subjects of the reaction NST type were placed into the ‘normal group’ and 23 ones of the suspicious NST type were placed into the ‘suspicious group’.

**FHR analysis**

After acquiring the FHR signals, the feature extraction procedure was followed. There are numerous methods for application of the foetal heart rate variation to the antepartum assessment of foetal well-being [5,6]. Although the recording parameters of the time domain used in this study have already been reported elsewhere for the prenatal period [7], it was considered justifiable to apply them to the third trimester of pregnancy when the difference in variation between active and quiet cycles or states becomes more pronounced with gestation [8].

The mean baseline (BL) value is as follows:

\[
mBL = \frac{1}{N} \sum_{i=1}^{N} BL(i)
\]

where \( N \) is the total number of the recording sample time pieces. Since this study was a long-term one with 72% recordings exceeding 16 h, \( N \) was set to 14 400, which corresponds to 1 h recording data.

The standard deviation of the BL value is:

\[
SD = \sqrt{\frac{1}{N-1} \sum_{i=1}^{N} (BL(i) - mean)^2}
\]

The heart rate variation (HRV) can be expressed as:

\[
HRV = \max_{i \in [1,T]} (FHR(i)) - \min_{i \in [1,T]} (FHR(i))
\]

where \( T \) is the length of short-term interval. According to the American College of Obstetricians and Gynecologists (ACOG), 0–5 beats per minute (bpm) is a small variation (SV), 6–25 bpm is a medium variation (MV), while the values exceeding 25 bpm correspond to the significant variation or large variation (LV).

The share of quiet sleep cycles (PQS) is defined as follows. Depending on the FHR variation, foetal sleep can be subdivided into quiet sleep and active sleep. Quiet sleep is the episode accord with long-term FHR variation (LTV) in at least 5 out of 6 continuous minutes not exceeding 30 milliseconds [5,9].

**Statistical analysis**

The Gaussian detection method was applied to the analysis of subjects to confirm that their parameters were normally distributed. Independent sample \( t \)-test, which compares the means between two unrelated groups on the same continuous dependent variable, was applied to the normal group vs. suspicious group, and then the correlation between gestational age, HRV and PQS was analysed. The quantitative differences between two types of foetuses were identified and compared. The statistical tests were performed using the SPSS 20.0 software package, where the value \( P<0.05 \) is regarded as statistically significant.

**Results and discussion**

There was a certain correlation between the mean baseline value and time. The mean value of the baseline for the lower state corresponded to 4 pm and to 2 am for the higher state. Moreover, there was an obvious decreasing trend from 10 pm to the next day’s 2 am, while the suspicious group’s mean baseline value was higher than that of the normal group by about 3 bpm.

Insofar as there are only 21 normal subjects and 23 suspicious subjects, which is insufficient for grouping by
GA, the differences in the mean baseline values according to GA were not compared.

The shares of each HRV range and the $P$-values for the normal and suspicious groups are presented in Table 1. The signal fragment is omitted if the signal lost rate exceeded 40%. Acceleration and deceleration fragments were eliminated before calculating the HRV range share. The normal group of foetuses exhibited a lower share in the SV range (35.96%) and a higher share in the MV range (60.64%), while the opposite trends were observed for the suspicious group with a higher SV-range share (48.86%) and a lower MV-range one (49.13%). In addition, the LV-range share for the normal group of foetuses (3.40%) was slightly higher than that of the suspicious one (2.00%). Meanwhile, all three feature values exhibited a statistically significant correlation between the normal and suspicious group, in particular, the $p$-value of the SV- and MV-range shares was less than 0.001, which implies a strong statistical correlation between these two types of foetuses.

Comparison of the relationship between the normal and suspicious groups is depicted in Figure 1, where the shares (proportions) of SV- and MV-ranges in the total variation are plotted along the ordinate $y$ axis, where blue box plot stands for the normal group, and the green one, for the suspicious group. Figure 2 illustrates the gradual increase in the SV share with GA. All three variation ranges exhibit significant differences between the normal and suspicious groups. A similar dependence of the MV share versus GA is depicted in Figure 3.

The normal group PQS parameter was smaller than that of the suspicious group, while there was no significant difference between the two groups. The GA and the PQS parameter exhibited a positive correlation in the normal group, with a Pearson coefficient of 0.552 ($P < 0.05$). No correlation between gestational age and the PQS parameter was found in the suspicious group.

### Table 1. Shares of different HRV ranges.

| HRV Range | 0 ≤ HRV ≤ 5 | 5 ≤ HRV ≤ 25 | HRV > 25 |
|-----------|-------------|--------------|----------|
| Normal    | 35.96%      | 60.64%       | 3.40%    |
| Suspicious| 44.86%      | 49.13%       | 2.00%    |
| $P$-value | <0.001      | <0.001       | 0.019    |

The GA and the SV-range share manifested a positive correlation in the normal group, with a Pearson coefficient of 0.685 ($P < 0.001$). A negative correlation was found between GA and the MV-range share with a Pearson coefficient of 0.623 ($P = 0.003$) and LV-range share with a Pearson coefficient of $-0.721$ ($P < 0.001$). In the suspicious group, no correlation between the GA and the share of any of the three ranges was revealed. In the third trimester, the SV shares of the normal foetuses increased with gestation, while their MV and LV ones decreased.

The normal group PQS parameter was smaller than that of the suspicious group, while there was no significant difference between the two groups. The GA and the PQS parameter exhibited a positive correlation in the normal group, with a Pearson coefficient of 0.552 ($P < 0.05$). No correlation between gestational age and the PQS parameter was found in the suspicious group.
In this study, long-term recordings were used to acquire the foetal heart rate features. The shares of three HRV ranges and PQS were extracted with their relationships with GA in the normal and suspicious groups. The study revealed a significant difference in the shares of different HRV ranges between foetuses from the normal and suspicious groups. HRV, as an important parameter, is widely used in obstetrics and gynaecology. Costa et al. [10] found that the HRV was helpful to distinguish foetal gender throughout most of GA. Russell et al. [11] studied the neonatal HRV to distinguish normal from diabetic pregnancy.

It is easy to perceive that the SV-range share in the normal group is smaller than in the suspicious one. In clinical, obstetrician and gynaecologist diagnoses, the foetal state in utero is assessed with HRV, acceleration and baseline. A foetus with too high an SV-range share and low HRM acceleration will be diagnosed as a suspicious one. The SV-range share demonstrates an opposite trend to the MV and LV ones. In addition, the SV-range share of normal foetuses increases with GA, while the GA and the PQS parameter exhibit a positive correlation in the normal group. This finding may indicate that foetus brain gradually develops with GA, so that its sleep cycles gradually become regular. Then, as the foetuses’ quiet sleep cycles become more frequent, their share in the SV range and PQS parameter increase gradually. Yiallourou et al. [12] studied the effects of intrauterine growth restriction on sleep and the cardiovascular system, so the PQS is also related with intrauterine growth restriction. No positive correlation between GA and the PQS parameter, as well as between GA and the SV or MV shares, was found in suspicious foetuses, indicating that the development of suspicious foetuses is worse than that of normal ones even though there are no significant differences between them.

The differences between the normal and suspicious groups were not significant and were indicated by the Apgar score and the pH value of umbilical cord blood. However, the consumption of medical resources in the suspicious group was much higher than that in the normal group. As the foetal heart rate electronic monitoring improves the sensitivity of diagnosis, many normal foetuses are wrongly diagnosed as suspicious ones. Finding and correcting the analysis of differences between the normal and suspicious groups will help to reduce the false positive rate and the consumption of medical resources.

If the foetal GA is 36–40 weeks, its type is assessed by the SV range share: if the share is 36.0% ± 9.8%, it can be considered a suspicious foetus, while the share of 48.9% ± 9.6% suggests that the foetus is normal. Extending the number of subjects will help to determine a more accurate threshold.

Traditionally, the average recording duration is about 40 min [13], or the recordings are extended to the maximum of 60 min [1]. The objectivity of parameters acquired via the short-term monitoring data might be quite low, due to the lack of collected information. A small variation rise revealed by short-term monitoring may indicate that the foetus experiences quiet sleep cycles rather than imply the occurrence of a foetal problem.

The central and vegetative nervous systems gradually develop with gestational age. The lower SV-range share and higher MV and LV ones in the normal group, as compared to the suspicious group, indicate more mature brain development of the normal foetuses. The SV-range share in the normal group exhibits a positive correlation with the gestational age, which implies that the former increases with the latter. It is consistent with the fact that gestational age and the PQS parameter exhibit a positive correlation in the normal group. The difference in variation between active and quiet cycles or states becomes more manifested with advancing gestation [8]. The number of quiet sleep cycles increasing with gestation causes the increase in the SV range share.

These rest–activity cycles were first observed at 23 weeks [8]. In this study, the gestational age of all subjects exceeded 30 weeks and all of them had quiet sleep cycles. The gestational age and the PQS parameter possess a positive correlation in the normal group.

Conclusions

The study revealed a significant difference in the shares of different HRV ranges between foetuses from the normal and suspicious groups. Intrapartum NST type can help decide whether to terminate a pregnancy. Extending the number of subjects to 30 per GA is needed for determining a more accurate threshold value to distinguish the normal and suspicious foetuses. The increase of the SV-range share and PQS parameter in the normal group share with advancing gestation is consistent with the known foetal brain development trend.

Disclosure statement

The authors declare no conflict of interest.

Funding

This research was funded by Bill & Melinda Gates Foundation [grant number OPP1148910] and Beijing Natural Science Foundation [grant number 7172015].
References

[1] Serra V, Bellver J, Moulden M, et al. Computerized analysis of normal fetal heart rate pattern throughout gestation. Ultrasound Obstet Gynecol. 2009;34:74–79.

[2] Georgoulas G, Stylios CD, Groumpos PP. Predicting the risk of metabolic acidosis for newborns based on fetal heart rate signal classification using support vector machines. IEEE Trans Biomed Eng. 2006;53(5):875–884.

[3] Gonçalves H, Ayres-de-Campos D, Bernardes J. The effect of gender, gestational age and behavioral states on fetal heart rate variability. Paper presented at: 8th Conference of the European Study Group on Cardiovascular Oscillations, Magnetism; 2014 May 25–28; Trento, Italy.

[4] Kupka T, Wrobel J, Jezewski J, et al. Evaluation of fetal heart rate baseline estimation method using testing signals based on a statistical model. Paper presented at: EMBS Annual International Conference; 2006 Aug 30–Sept 3; New York, USA.

[5] Dawes GS, Moulden M, Redman CWG. Improvements in computerized fetal heart rate analysis antepartum. J Perinat Med. 1996;24:25–36.

[6] Task force of the European Society of cardiology and the North American Society of pacing and electrophysiology, heart rate variability. Standards of measurements, physiological interpretation, and clinical use. Eur Heart J. 1996;17:354–381.

[7] Magenes G, Signorini MG, Arduini D. Classification of cardiococographic records by neural networks. IEEE Neural Networks. 2000;3:637–641.

[8] Pillai M, James D. The development of fetal heart rate patterns during normal pregnancy. Obstetrics & Gynecology. 1990;76:812–816.

[9] Pardey J, Moulden M, Redman CWG. A computer system for the numerical analysis of nonstress tests. Am J Obstet Gynecol. 2002;186:1095–1103.

[10] Costa CA, Cruz J, Campos DA, et al. Gender-specific reference charts for cardiococographic parameters throughout normal pregnancy: a retrospective cross-sectional study of 9701 fetuses. Eur J Obst Gynecol Reprod Biol. 2016;199:102–107.

[11] Russell NE, Higgins MF, Kinsley BF. Heart rate variability in neonates of type 1 diabetic pregnancy. Early Hum Dev. 2016;92:51–55.

[12] Yiallourou SR, Wallace EM, Miller SL. Effects of intrauterine growth restriction on sleep and the cardiovascular system: the use of melatonin as a potential therapy. Sleep Med Rev. 2016;26:64–73.

[13] Lucchini M, Signorini MG, Fifer WP, et al. Multi-parametric heart rate analysis in premature babies exposed to sudden infant death syndrome. USA: Columbia University College of Physicians & Surgeons; 2014.