Assessment of Fetal Autonomic Nervous System Activity by Fetal Magnetocardiography

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Abstract

Aim: To clarify the significance of heart rate variability for the evaluation of an autonomic nervous system (ANS) in the normal fetus using fetal magnetocardiography (FMCG).

Methods: Subjects consisted of normal pregnancy (n = 35) at 28–39 weeks gestation. FMCG was recorded using 64-channel magnetocardiography (MCG) in a magnetically shielded room. The QRS interval was derived from signal-averaged MCG. The R–R interval variability induced by an R-wave trigger was eventually adopted to calculate for time-domain and frequency domain analysis. The power spectrum in the frequency domain was derived from frequency-field components using the maximum entropy method of fetal heart rate variability. Based on frequency analysis, the ranges of the LF and HF domains were defined as 0.01–0.15 and 0.15–0.4 Hz, respectively. We defined a coefficient of variance (CVRR) as an index of parasympathetic activity, and defined a low frequency/high frequency (LF/HF) ratio as a sympathetic activity.

Results: The value of CVRR in the normal pregnancy group displayed a slight increasing trend with gestational age (y = 1.77 + 0.10x; r = 0.32). In contrast, the LF/HF ratio in the normal pregnancy group clearly increased over the gestational period (one-way ANOVA: P = 0.003).

Conclusions: Analyses based on the time and frequency domains of heart rate variability using FMCG enable an evaluation of fetal ANS activity. Sympathetic nervous activity increased with gestational age in the normal pregnancy group.

Keywords: fetal magnetocardiography, heart rate variability, autonomic nervous system, development

Introduction

The frequently encountered high-risk cases of pregnancies and parturitions, the early detection and causative reference of neurological complications are sometimes very critical in assessing fetal well-being. Although deficient in certain aspects, routine fetal monitoring is currently performed using ultrasonography and cardiotocography. Thus little is known about the interdependency of standard fetal heart rate variability measures prenatally.¹ Magnetocardiography (MCG) is a safe and non-invasive method that employs a superconducting quantum interference device (SQUID) to facilitate a 3-dimensional analysis of the micro-magnetic field (10⁻¹² tesla) generated by phenomenal electric activities of the heart. Recent applications of fetal MCG (FMCG) have yielded details of acquired QT prolongation syndrome, supraventricular tachycardia, and various fetal arrhythmias.²⁻⁹

Attention has recently focused on spectral analysis of heart rate variability as a method for evaluating fetal well-being; for example, the efficacy of analyses of the coefficient of R-R interval variability (CVRR), and frequency domain values (low-frequency (LF)/high-frequency (HF) ratio). The LF/HF ratio in a supine
resting posture has been suggested for the evaluation of autonomic nervous system (ANS) activities.\textsuperscript{10,11} The methods of ultrasonography and cardiotocography, which are incapable of measuring CV\textsubscript{RR}, LF/HF ratio, and various fetal heart-rate variability analyses, can be improved upon with FMCG, thereby enabling these indices to be determined. In the present study, we evaluated the significance of heart rate variability as an actual autonomic nervous system development of normal fetuses at 28–37 weeks of gestation using FMCG.

**Subjects and Methods**

**Subjects**

Subjects enrolled in the present study were normal pregnancies (n = 35) at 28–39 weeks of gestation that visited our hospital as either outpatients or inpatients between January 2004 and July 2005. In the normal pregnancy group, fetuses were born at term and without any abnormal neurological signs. Written informed consent was obtained from all subjects after being briefed about the clinical study, which was approved by the Ethics Committee of the School of Medicine, Iwate Medical University (H14-33, H17-2).

**Equipment**

To obtain FMCG measurements, pregnant volunteers assumed a supine position on a bed and were scanned with a 64-channel MCG sensor (Prototype, SQUID sensor, Hitachi High-Technology Co. Ltd., Tokyo, Japan) installed in a magnetically shielded room (Fig. 1). The position of the fetus was determined with ultrasonography, using the navel and pubic symphysis as reference coordinates. The magnetic field in the z direction (Bz) adjacent to the body surface was monitored continuously for 5 minutes. A total of two or three measurements were obtained in this manner. Because the detected Bz is a summation of signals from fetal and maternal sources, the maternal QRS waveform was subtracted from the detected Bz to derive the actual Bz value. Fetal heart rhythm (approximately 700 beats) was measured for 5 minutes, and the average heart rate of each case was used to derive the FMCG. The initial and termination values of PQ, QRS, and QT were defined by the maximum points of the first derivate of dF/dt.

CV\textsubscript{RR} was calculated as follows:

\[
SD = \sqrt{\frac{1}{n} \sum_{i=1}^{n} (Di - \overline{M})^2}
\]

and

\[
CV_{RR} = \frac{SD}{\overline{M}} \times 100 \text{(\%)}
\]

where \(n\) and \(Di\) represent the number of R–R intervals and the mean of approximately 700 R–R intervals, respectively, and \(\overline{M}\) represents the total mean of the respective \(Di\).

The power spectrum in the frequency domain was derived from frequency-field components using the maximum entropy method of fetal heart rate variability. Based on frequency analysis, the ranges of the LF and HF domains were defined as 0.01–0.15 and 0.15–0.4 Hz, respectively. The respective power values were derived to yield the LF/HF ratio. Note that the LF/HF ratio is taken as a sympathetic activity of ANS.\textsuperscript{12,13}

**Statistical analysis**

Data were analyzed using StatView for Windows Ver. 5.0 (SAS Institute Inc., Cary, NC, U.S.A.). The relationships among CV\textsubscript{RR}, LF/HF, and gestational age in each group were analyzed by linear regression, while inter-group changes in CV\textsubscript{RR} and LF/HF over the gestational period in each group were verified by one-way ANOVA.

**Results**

The normal pregnancy group was divided into three groups for classifying one-way ANOVA analysis of CV\textsubscript{RR} and LF/HF as follows: Group A, 28–31 weeks of pregnancy (8th month of pregnancy); Group B, 32–35 weeks of pregnancy (9th month of pregnancy); and Group C, 36–40 weeks of pregnancy (10th month of pregnancy).

The value of CV\textsubscript{RR} in normal pregnancy showed a slight increased trend with gestational age (\(y = 1.77 + 0.10x; r = 0.32\)) (Fig. 2). Inter-group changes in CV\textsubscript{RR} in normal pregnancy showed no significant deference to the gestation period (one-way ANOVA: \(P = 0.28\)) (Fig. 3).

The value of LF/HF in the normal pregnancy group showed an increase with gestational age (\(y = 0.19 + 0.04x; r = 0.49\)) (Fig. 4). Inter-group
Figure 1. A monitoring device for magnetocardiography (MCG) incorporating a 64-channel SQUID apparatus in a magnetically shielded room.

Figure 2. Correlation between the coefficient of variance (CV_{RR}) and gestational age in normal pregnancy.

$$y = 1.77 + 0.10x; \quad r = 0.32$$
**Figure 3.** Inter-group changes in the coefficient of variance (CV_{RR}) during normal pregnancy. Group A; 28–31 weeks of pregnancy, Group B; 32–35 weeks of pregnancy, and Group C; 36–40 weeks of pregnancy.

CV_{RR} (%)

| Group   | CV_{RR} (%) | n  |
|---------|-------------|----|
| A       | 4.83 ± 1.21 | 12 |
| B       | 4.84 ± 0.57 | 5  |
| C       | 5.43 ± 1.07 | 18 |

One-way ANOVA: P = 0.28

**Figure 4.** Correlation between the low frequency/high frequency (LH/HF) ratio and gestational age in normal pregnancy.

\[ y = 0.19 + 0.04x; r = 0.49 \]
changes in LF/HF in the normal group increased significantly according to the gestation period (one-way ANOVA: P = 0.003) (Fig. 5).

Discussion
Recent advances in medical electronics have enabled various fetal parameters in the field of perinatal medicine to be obtained in greater detail and with higher precision. Current improved versions of ultrasonography devices can provide detailed evaluation regarding morphology and/or blood flow dynamics. To assess fetal ANS function, Shields and Schifrin evaluated fetal heart rate variability derived from fetal cardiotocography and respiratory movements. More than 90% of fetal asphyxia cases were detected by abnormal heartbeat patterns using cardiotocography. Thus, cardiotocography is an indispensable tool that is routinely employed in clinical obstetrics; however, even when abnormal heartbeat patterns are detected, the combined use of ultrasonic Doppler and biophysical profile analysis does not improve the ability to identify undiagnosed cases of asphyxia. These conventional methods are yet to objectively and reliably evaluate functional development of the fetal autonomic nervous system; they are also unable to consistently achieve prenatal diagnosis of conditions that result from abnormal fetal autonomic nervous system development, such as cerebral palsy. As a result, unnecessary obstetric interventions are encountered, and the rate of cesarean section continues to increase without any decrease in the incidence of fetal central nervous system impairments, especially cerebral palsy. This problem indicates the need for a novel method for prenatal diagnosis.

In the present study, we developed a FMCG by modifying our recently developed 64-channel MCG. The special features of MCG make it possible for the device to perform a 3-dimensional analysis of the magnetic field generated by the

![Figure 5](image-url)

**Figure 5.** Inter-group changes in the low frequency/high frequency (LH/HF) ratio during normal pregnancy. Group A; 28–31 weeks of pregnancy, Group B; 32–35 weeks of pregnancy, and Group C; 36–40 weeks of pregnancy.
Phenomenal electric activities of the heart in both fetuses and adults. FMCG is an extremely safe and non-invasive method for monitoring fetal cardiac activities. To date, numerous studies have used FMCG to analyze fetal arrhythmias. Although analyses of heart rate variability have been attempted on fetal autonomic nervous system functions using FMCG, little has been established using this technique. LF and HF bands have been defined according to adult standard. Recently, for fetal heart rate variability, different frequency ranges were proposed from one group. However, there is no apparent standard definition for the fetal heart rate variability yet.

In the present study, FMCG signals were generally too weak to enable a precise analysis of fetal ANS activity to be performed prior to 28 weeks of pregnancy. To advance the development of this method, we undertook the following studies; elucidation of the developmental stages of the fetal autonomic nervous system over a period of 39 weeks of pregnancy. As a result of measurements, CVRR value, a value that reflects parasym pathetic nervous system (PSN) activity, exhibited a slight increasing trend with gestational age in the normal pregnancy group. In addition, we defined a value of the LF/HF ratio as the sympathetic nervous system (SNS) activity or balancing factor between the SNS and the PNS activities. The LF/HF ratio showed a clear increase with gestational age in the normal pregnancy group. It is understood that fetal ANS function develops as gestation progresses. These results are consistent with ultrasound analyses of the fetal mouthing movement interval and eye-movement phase patterns, in which major changes are seen to occur at around gestational weeks 28–33. This evidence from earlier studies is consistent with the results of the present study. Our results revealed that the maturation process, especially in SNS activity or the balancing factor between SNS and PNS activities, changes dramatically from 28–39 weeks gestation. For the fetus, therefore, it is very important to avoid preterm delivery, not only in terms of body size and organic maturation but also for the functional development of ANS.

The development pattern of ANS in the fetal period may become one of the important indices for prenatal management in the near future. In IUGR cases, both the difference in fetal size and other obstetric risks are higher, and the correlation dimension decreases when compared with the normal pregnancy group; that is, the heart rate coordination system is non-versatile and highly susceptible to stress. In brief, it is critical to differentiate on grounds of perinatal management whether a fetus has low body weight alone, or whether it also has endogenous functional issues.

Study limitation: The sample size was small in this study. There will be needed a further study for the definite termination of the autonomic activity in the fetus.

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