Development and Significance of a Fetal Electrocardiogram Recorded by Signal-Averaged High-Amplification Electrocardiography

Risa Hayashi,1 MD, Kenji Nakai,2 MD, Akimune Fukushima,1 MD, Manabu Itoh,3 MD, and Toru Sugiyama,1 MD

SUMMARY

Although ultrasonic diagnostic imaging and fetal heart monitors have undergone great technological improvements, the development and use of fetal electrocardiograms to evaluate fetal arrhythmias and autonomic nervous activity have not been fully established. We verified the clinical significance of the novel signal-averaged vector-projected high amplification ECG (SAVP-ECG) method in fetuses from 48 gravidas at 32-41 weeks of gestation and in 34 neonates. SAVP-ECGs from fetuses and newborns were recorded using a modified XYZ-leads system. Once noise and maternal QRS waves were removed, the P, QRS, and T wave intervals were measured from the signal-averaged fetal ECGs. We also compared fetal and neonatal heart rates (HRs), coefficients of variation of heart rate variability (CV) as a parasympathetic nervous activity, and the ratio of low to high frequency (LF/HF ratio) as a sympathetic nervous activity. The rate of detection of a fetal ECG by SAVP-ECG was 72.9%, and the fetal and neonatal QRS and QTc intervals were not significantly different. The neonatal CVs and LF/HF ratios were significantly increased compared with those in the fetus. In conclusion, we have developed a fetal ECG recording method using the SAVP-ECG system, which we used to evaluate autonomic nervous system development. (Int Heart J 2009; 50: 161-171)

Key words: Fetal ECG, Newborn ECG, Signal-averaged ECG, Autonomic nervous system, Heart rate variability

WITH the advances in perinatal medicine, we can now obtain fetal information before birth. Ultrasonic diagnostic imaging apparatuses can be used to diagnose various blood stream abnormalities in fetal malformations.1,2 Fetal heart rate monitoring is also useful for detecting asphyxia. While such advances in

1 Department of Obstetrics and Gynecology, 2 Internal Medicine of Dentistry, Iwate Medical University, Morioka, Iwate and 3 ICS Co., Ltd., Morioka, Iwate, Japan.

Address for correspondence: Kenji Nakai, MD, Internal Medicine of Dentistry, Iwate Medical University, 19-1, Uchimaru, Morioka, Iwate 020-8505, Japan.

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medical technology have greatly improved perinatal mortality rates, the complete functionality of the fetal central nervous system (CNS) cannot yet be fully determined.

Two of the most important fetal/neonatal disorders involving the nervous system are cerebral palsy (CP) and sudden infant death syndrome (SIDS). About 10% of CP cases are caused by hypoxemia at the time of delivery. However, the time of onset and the cause of CP remain unclear. Conventional studies with cardiotocograms (CTG) reveal abnormal heart-beat patterns in more than 90% of non-reassuring fetal status. However, ultrasonic Doppler and biophysical profiles do not completely detect CP at the prenatal stage. Furthermore, unnecessary obstetric medical intervention often results in an increased Caesarean section rate, and the frequency of CP at birth does not decrease with such interventions.

One cause of SIDS is an undeveloped neonatal autonomic nervous system (ANS). In addition, lethal cardiac arrhythmias such as long QT syndrome may also contribute to SIDS onset. Thus, investigating ANS development in the fetal and newborn period may be helpful in understanding or diagnosing these disorders.

The evaluation of fetal physiology before birth, including lethal cardiac arrhythmia and ANS, enables the administration of appropriate perinatal medical care. In 1906, Cremer recorded the first fetal ECG using a string galvanometer; however, the forms of the P, QRS, and T waves were not clear. In 1954, Davis and Meares et al first demonstrated clear P wave, QRS-complex, and T wave morphologies on the fetal ECG. Although their measurement method and signal analysis have not been established, there have been several reports of successful fetal ECGs. Fukushima, et al noninvasively evaluated the fetal ANS using 64-channel (64-ch) magnetocardiography (MCG), and found that fetal ANS activity greatly changed over the 9-month gestation period. The MCG is highly sensitive for detecting fetal electrical phenomena, but is limited in terms of its use as a bed-side measurement or in the emergency room, since it requires a magnetic shield room. In addition, Nakai, et al recently developed signal-averaged vector-projection ECG (SAVP-ECG) as a way to detect high-frequency low-amplitude signals and myocardial repolarization abnormalities.

In the present study, we verified several aspects and examined the clinical usefulness of SAVP-ECG in perinatal medical care. First, we verified fetal and neonatal use of the SAVP-ECG as a detection method for fetal arrhythmia. We then verified the use of an analytical method for determining heart rate variability and changes in ANS activity, including the significance of the ratio of low and high frequencies of the heart rate variability (LF/HF ratio) of the fetus and newborn.
METHODS

Subjects: Subjects consisted of 48 gravidas at 32-41 weeks of gestation, who were hospitalized in the obstetrics and gynecology department of Iwate Medical University from April 2007 through May 2008. The subjects were divided into 3 groups based on gestation: 32 weeks to 35 weeks 5 days (designated as “< 36 weeks”), 36 weeks and older (designated as “≥ 36 weeks”), and neonates. We measured 34 neonatal ECGs (within 1 week of birth). Volunteers signed written consent forms that had been approved by the Ethics Committee of Iwate Medical University.

Procedure: We used the novel prototype SAVP-ECG system, with a high resolution (0.076 μV/bits) and sampling rate (2000 Hz/s) (Figure 1). A modified X,Y,Z-leads system was used to obtain fetal ECGs (Figure 2A). Electrodes were placed on the mothers at the right (+) and left (-) lower points of the abdomen for X instruction, right lower point (+) and left higher point (-) of the abdomen for Y instruction, and at a zone where fetal heart sounds could be distinctly recognized for Z instruction. Fetal ECGs were recorded for 5 minutes by this modified X,Y,Z-leads system. We used a silver-silver argentic chloride magnet electrode (TE-18 series, Fukuda Denshi Co. Ltd., Tokyo) for fetal ECG measurements and an ECG electrode (Red Dot, 3M Health Care, Tokyo) for neonatal ECG measurements.

Noise was removed from the original signals via low-level (0.5 Hz) and high-level (25 Hz) removal filters. We made a template of the QRS signal of the mother, extracted the fetal signal, and removed the maternal QRS wave. We then
added 300-500 heart-beats by triggering the fetal QRS complex. The heart rate (HR) was determined from the equation \( \text{HR} = \frac{60000}{\text{R-R interval}} \); where “R-R” is the time interval between an R wave and the following R wave. We measured the PQ, QRS, and QT intervals from a signal-averaged fetal ECG, and determined the inflection points for P, QRS, and T waves by the first derivative. The QT interval was corrected by use of Bazett’s equation. We also determined the heart rate variability, an index of parasympathetic activity, as the coefficient of variance (CV) from the following equation: \( \text{CV} = \frac{\text{SD} \sqrt{\text{R-R}}} \). As an index of the frequency, we used a Fast-Fourier transform (FFT) in the neighborhood of 0.1 and 0.3 Hz to perform a spectral analysis of R-R changes. We determined the ratio (LF/HF ratio) of the greatest peaks of the low and high frequency parameters as an index of sympathetic nervous activity.\(^{13}\) The Mason-Likar lead system was used for neonatal ECG recordings (Figure 2B). We measured 34 neonatal ECGs (within 1 week of birth). From each fetal and newborn ECG, we measured each index (HR, CV, QRS, LF/HF ratio) and verified the changes in the fetal and newborn periods.

Using multivariable logistic analysis (SPSS, Tokyo), we determined which fetal/maternal conditions yielded high quality ECGs. In particular, we tested the following conditions: the number of weeks of gestation (< or ≥ 36 weeks), fetal weight estimate (< or ≥ 2500 g), placental position (anterior or posterior), maternal body mass index (BMI) (< or ≥ 26), fetal heart sound, and abdominal wall straining as uterine contraction.
Statistical analysis: Each index is represented as the mean ± standard deviation. One-way ANOVA was used to determine the significance of the time-course for the CV LF/HF ratio; a $P$-value < 0.05 was regarded as significant.

RESULTS

Representative fetal ECGs are shown in Figure 3. The upper section (Figure 3A) shows a representative maternal ECG obtained using the modified X,Y,Z-leads system, in which a low amplitude fetal ECG signal was recorded with the other noise. The resulting ECG after removing the maternal QRS waves, which were obtained after filter processing, is found in the lower panel (Figure 3B). A signal-averaged fetal X,Y,Z-leads ECG and its first derivative waves are shown in Figure 4A. We identified the inflection points of the P, QRS, and QT sections.

Figure 3. A: Maternal ECG by a modified XYZ-leads system. B: Fetal ECG.
from the first derivative wave patterns. The rate of detection of a fetal ECG by the SAVP-ECG method was 72.9% (35 out of 48 cases). When reviewed according to the weeks of gestation, this rate was 60% for the < 36 weeks group and 74% for the ≥ 36 weeks group. Fetal and neonatal SAVP-ECGs are shown in Figures 4A and 4B.

The average fetal/neonatal QRS interval was 57 ± 2 ms for the < 36 weeks group, 52 ± 5 ms for the ≥ 36 weeks group, and 52 ± 4 ms for the neonatal group. The QTc interval was 391 ± 16 ms for the < 36 weeks group, 378 ± 22 ms for the ≥ 36 weeks group, and 388 ± 22 ms for the neonatal group. No significant differences were observed in the QRS or QTc intervals between the fetal and neonatal periods (Table I). The average neonatal CV (8.3 ± 3.7%) was significantly increased compared to those in 32-35 weeks (3.7 ± 0.8%) and ≥ 36 weeks (4.2 ± 1.9%) fetal groups (Table I). The LF/HF ratios for the < 36 weeks, ≥ 36 weeks, and neonatal groups were 0.98 ± 0.38, 1.17 ± 0.34, and 1.42 ± 0.30, respectively; this ratio was significantly higher in the neonatal group than in the fetal groups (Table I). Representative fetal and neonatal heart rate variability,

**Table I.** Summary of QRS and QTc intervals, CV, and LF/HF ratio at gravid 32 weeks - 35 weeks, 5 days; gravid ≥ 36 weeks; and the neonatal period

<table>
<thead>
<tr>
<th></th>
<th>Gravid 32 weeks -35 weeks, 5 days</th>
<th>Gravid ≥ 36 weeks</th>
<th>Neonate</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>5</td>
<td>43</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>143</td>
<td>130</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>QRS interval</td>
<td>57 ± 2 ms</td>
<td>52 ± 5 ms</td>
<td>52 ± 4 ms</td>
<td></td>
</tr>
<tr>
<td>QTc interval</td>
<td>391 ± 16 ms</td>
<td>378 ± 22 ms</td>
<td>388 ± 22 ms</td>
<td></td>
</tr>
<tr>
<td>CV</td>
<td>3.7 ± 0.8%</td>
<td>4.2 ± 1.9%</td>
<td>8.3 ± 3.7%</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>LF/HF</td>
<td>0.98 ± 0.38</td>
<td>1.17 ± 0.34</td>
<td>1.42 ± 0.30</td>
<td>P &lt; 0.005</td>
</tr>
</tbody>
</table>

**Figure 4.** A: Fetal ECG by a modified XYZ-leads system and the first derivative wave pattern of the fetal ECG. We identified the reflection points of the P, QRS, and QT sections by the first derivative of the fetal ECG. B: Neonatal ECG.
CV, and frequency analysis results are shown in Figures 5A and 5B.

We performed a multivariable analysis of the relationship between ECG recording and many gravid variables, including the number of weeks of gestation, estimated fetal weight, placental position, maternal BMI, fetal heart sound, and nature of uterus constriction. This analysis revealed a possible relationship between the fetal heart sounds, gestational period, and the degree of the nature of uterus constriction and the quality of the ECG; however, no statistically significant differences were found among these parameters shown in Table II.

**Table II. Parameters for Multivariate Analysis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P value</th>
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<tbody>
<tr>
<td>Weeks of pregnancy</td>
<td>0.375</td>
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<tr>
<td>Placental position</td>
<td>1.00</td>
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<tr>
<td>Maternal BMI</td>
<td>0.736</td>
</tr>
<tr>
<td>Uterus constriction</td>
<td>0.415</td>
</tr>
<tr>
<td>Estimated fetal weight</td>
<td>0.415</td>
</tr>
<tr>
<td>Fetal heart sound</td>
<td>0.165</td>
</tr>
</tbody>
</table>

BMI indicates body mass index.

**Discussion**

**High amplification SAVP-ECG system:** When obtained at 32 weeks of gestation or later, the average detection ratio of a fetal ECG using the novel high amplification SAVP-ECG method was 72.9%. This prototype SAVP-ECG could be used to evaluate QT intervals, which are related to the repolarization abnormality caused by lethal cardiac arrhythmia. In addition, this system also allowed the active evaluation of the fetal and neonatal sympathetic and parasympathetic nervous systems, as indicated by changes in the LF/HF ratio and CV.
**Fetal ECG recording:** The amplitude of a fetal heart signal is approximately 20-50μV, which is about 1/20th of that in the adult. Generally, it is difficult to obtain a fetal ECG recording, due to influences from the maternal ECG and electromyogram components from the maternal abdominal wall and fetal movements. Stinstra, *et al* reported that barriers, including the vernix, amniotic fluid, uterine muscle, placenta, and the maternal abdominal wall, are the major hurdles associated with measuring fetal ECGs. Some studies have successfully detected lethal cardiac arrhythmias with fetal MCGs. However, while highly sensitive, such devices are large and unsuitable for ICU and emergency room bedside recordings.

Kimura, *et al* developed a high-speed, nonlinear state space projection (FNSSP: Fast Nonlinear State Space Projection) and a new Bryant signal algorithm (BSSR: Blind Source Separation with Reference signal) using a supersonic wave Doppler reference signal. They placed 12 electrodes on the body of each gravida, crowded around the fetus. From a compound signal induced by the maternal abdominal wall, they could remove the maternal ECG components by reproducing a maternal vector and extracting the three-dimensional fetal heart signals.

The SVAP-ECG, which consists of a PC with an originally developed software program and an input box, enables the bedside examination of a fetal ECG. The foremost characteristics of this prototype SVAP-ECG are its excellent amplification and resolution abilities. Using this system, one can record inductive modified X,Y,Z-leads ECGs, 12-lead standard ECGs, and 187-ch vector-projected ECGs by signal processing. We used a modified X,Y,Z-leads ECG with 5 leading electrodes for fetal ECG recording, and removed the noise component from the source signal with two kinds of filters. We then removed the maternal QRS complex and extracted the fetal signal. We obtained a fetal ECG after signal-averaging 300-500 heart beats by triggering the QRS complex of the fetal signal. In its present form, visual observation is required to confirm the fetal ECG, because complete automatic recognition of fetal signals of the QRS complex is difficult. Finally, multivariate analysis indicated that the gestational period, ability to detect fetal heart sounds, and pregnancy-related abdominal wall straining might affect the ability to detect a fetal ECG.

This prototype SAVP-ECG can be used to evaluate fetal ANS activity. It can also be used to map the body surface of the newborn and maternal heart, as can be performed by 187-ch ECGs to evaluate myocardial injury. In addition to the fetus, we can also evaluate the electrical phenomena and myocardial injury of neonatal and maternal hearts at the same time. In other words, using this prototype SAVP-ECG, a “heart medical examination” for the mother and child during the gravid/perinatal period may be possible, enabling the early evaluation of
childhood cardiomyopathy and maternal myocarditis or myocardial injury.\(^{18}\)

**Clinical applications:** Intrauterine death (IUFD: Intrauterine fetal death) occurs when a fetus dies before delivery, regardless of the gestational period. IUFD may be caused by many fetal and related abnormalities; however, there are also many unidentified causes of IUFD.\(^ {19}\) In particular, IUFD in late gestation may be caused by cardiac arrhythmia. SIDS is another disorder that has no one clear, specific cause. The frequency of SIDS is estimated to be about 600-700 per year, corresponding to ~ 1 in every 2000 births (0.05%). Several possible causes for SIDS have been proposed, including specific sleep postures (sleep sharing, soft bedding), environmental conditions (passive smoking, bottled milk, malignant hyperthermia), and birth situations (prematurity).

Recent advances in the molecular biology and pathophysiology of congenital long QT syndrome, a genetic abnormality associated with lethal cardiac arrhythmias that lead to sudden death, have led to the discovery that lethal cardiac arrhythmias may also be potential causes of IUFD and SIDS.\(^ {9}\) Schwartz, et al reported that QT interval prolongation at one week after birth is strongly related to the probability of SIDS onset.\(^ {9}\) Fetal ventricular tachycardia (torsade de pointes) has also been observed by MCG.\(^ {10}\) The prototype ECG described here could be used to diagnose repolarization abnormalities of the QT interval in the fetal and newborn period, and may therefore be used to evaluate the risk of cardiac arrhythmia-related death during the perinatal period.

The incidence of CP at the time of birth is reported to be an average of 2 cases per 1000 live births. The causes of CP include unknown factors during pregnancy (39%), congenital abnormalities (11%), and factors related to delivery (8%).\(^ {20}\) The prenatal diagnosis of disorders related to cerebral function is an important concern for perinatal medical care. Recently, the evaluation of fetal brainstem function by auditory evoked fetal magnetoencephalogram (MEG) was reported.\(^ {21}\) Because fetal evoked MEGs may be difficult to perform as a general clinical application, we reviewed the significance of fetal heart rate variability for evaluating fetal ANS activity. Using a 64-ch MCG, Fukushima, et al found that the activity of the sympathetic and parasympathetic nervous systems, as evaluated from the LF/HF ratio, were enhanced at gestational ages of 32 weeks and later,\(^ {13}\) consistent with previous reports of a conversion point at 32 weeks of gestation.\(^ {22,23}\) We found that the ANS activity, as evaluated by the CV and LF/HF ratio using SAVP-ECG, was remarkably enhanced just after birth. Akselrod, et al discovered characteristic 0.1-Hz and 0.3-Hz frequency band levels (spectral peaks) in a spectral analysis of the heart rate variability in animals. The spectral peak size varied based on the ANS activity and the use of pharmacological agents.\(^ {24}\) The 0.1-Hz component may reflect the arterial blood pressure, which involves the medulla oblongata, the efferent pathway of the sympathetic nervous
Based on their concept, we speculate that ANS activity may be evaluated from the spectral analysis of heart rate variability.

In this study, we proposed the value of CV from time-domain analysis of heart rate variability as an index of parasympathetic nervous activity, and the LF/HF ratio from the frequency analysis of heart rate variability as a sympathetic nervous activity. We determined the LF/HF ratio from the greatest peaks in the neighborhood of 0.1 and 0.3 Hz. The mean values of CV and LF/HF ratio in normal fetuses in gravida > 36 weeks were 4.2% and 1.17, respectively. Samejima, et al evaluated the relation among the heart rate pattern under CTG and umbilical blood gases and cerebral palsy. They reported that the decreased variability of heart rate pattern correlated with decreased umbilical pH. They suggested that CP caused by intrapartum asphyxia was restricted under CTG. There has been no previous report of the relation between the heart rate variability by fetal ECG and an incidence of CP. In the future, we will investigate abnormal neural activity using fetal ECG.

Conclusions: By analyzing fetal cardiac electrical phenomena, SAVP-ECG may be used to detect lethal arrhythmias, repolarization abnormalities, and ANS activity. This method may therefore permit “maternal and fetal-neonatal medical examinations” in place of the conventional “gravida medical examinations” of the perinatal period.

References


