ORIGINAL ARTICLE

Nonreassuring Fetal Heart Rate Decreases Heart Rate Variability in Newborn Infants

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Background: Nonreassuring fetal status (NRFS) refers to a compromised fetal condition which implies hypoxia. The influence of intrapartum hypoxia on autonomic nervous system function in early postnatal life is unknown. This study explored the influence of NRFS on the heart rate variability (HRV) of newborn infants.

Methods: Singleton newborn infants delivered through Cesarean delivery (CD) with indications of elective purpose (n = 32), dystocia (n = 29), or NRFS (n = 22), and through vaginal birth (VB) (n = 80) were consecutively collected. HRV parameters including standard deviation of average NN intervals (SDANN), low frequency (LF), high frequency (HF), LF%, HF%, and total power (TP), were obtained for analysis in 3 days postpartum. An independent t-test or one-way ANOVA was used to compare differences in numeric data.

Results: SDANN, HF, HF%, and TP of newborn infants in the VB group were significantly higher than those in the CD group. The NRFS group had significantly lower SDANN, HF, and TP than those of the elective group, and significantly lower HF, HF%, and TP than those of the dystocia group.

Conclusions: Newborn infants delivered through Cesarean section had lower HRV, especially those who experienced NRFS during labor. The long-term effects of changes of HRV in neonates require further evaluation.

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electronic fetal monitor; heart rate variability; newborn infants; nonreassuring fetal status

Nonreassuring fetal status (NRFS) refers to a compromised fetal condition before or during childbirth. It is commonly used to describe fetal hypoxia.[1,2] NRFS is an emergent condition, which threatens fetal wellbeing if the underlying causes are not treated or if the fetus is not promptly delivered. Delay delivery of babies experiencing NRFS can cause significant deterioration of cord artery pH and base excesses.[3] Though severe acidosis slightly increases neonatal mortality, the predictive value of acidosis for neurological sequelae in term neonates remains poor.[4]

NRFS can be detected via reduced fetal activity, changes in the fetal heart rate, the presence of meconium in the amniotic fluid, or fetal scalp blood sampling showing a pH of $\leq$7.2.[5] During labor and delivery, the most commonly used method in evaluating fetal wellbeing is electronic fetal monitor (EFM). It is a screening test for identifying babies with acute or chronic fetal hypoxia or those at risk of developing such hypoxia.[6] Fetal heart rate patterns on EFM are usually defined by the characteristics of baseline, variability, acceleration, and deceleration. The presence of abnormal fetal

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heart rate patterns implies that fetal acidemia could have happened.[7,8]

In adults, heart rate variability (HRV) has been widely used to assess autonomic nervous system function by analyzing the variations in the beat-to-beat intervals on electrocardiography (ECG). Reduced HRV has been shown to be a predictor of mortality after myocardial infarction,[9] and associated with increased morbidity of cardiovascular disease, diabetes, and various pathologic conditions.[10] In infants, HRV increases with gestational and early postnatal age.[11] Attenuation of HRV was reported in neonates and infants with respiratory distress syndrome,[12] periventricular hemorrhage,[13] and fetal asphyxia.[14]

Though correlations between intrapartum hypoxia and neurological sequelae are controversial,[15] no study has examined the influence of intrapartum hypoxia on autonomic nervous system function in early postnatal life. This study was designed to explore the influence of NRFS, as depicted by EFM, on the HRV of newborn infants.

METHODS

Subjects

This prospective study was conducted in a medical center in Taiwan in 2010–2012. Singleton newborn infants delivered through Cesarean delivery (CD) with indications of elective purpose (n = 32), dystocia (n = 29), or NRFS (n = 22) were consecutively enrolled. In comparison, newborns who were delivered through vaginal birth (VB) (n = 80) during the same study period were also collected. Cases whose mothers were given antibiotics, oxytocin, or analgesics in labor, or were complicated with diabetes, hypertension, or other systemic disease were excluded from the study. Newborn infants who were intubated, jaundiced, given medications, or born prior to 37 weeks were also excluded. The study was approved by the Ethics Committee of the hospital. Informed consent was obtained from all parents.

Elective CD refers to a planned Cesarean section executed prior to labor at the request of a pregnant women. Dystocia indicates difficult childbirth or prolonged labor course. NRFS was diagnosed in the presence of a abnormal pattern of intrapartum EFM, which included a baseline heart rate of <120 or ≥ 160 beats/min for more than 10 minutes, persistence of HRV of <5 beats/min for ≥ 10 minutes, severe variable decelerations or severe repetitive early decelerations, prolonged decelerations of ≥ 2 minutes, and late decelerations in ≥ 3 consecutive contractions.[8] In this study, CD was universally conducted under spinal anesthesia. An episiotomy was performed under local anesthesia for all VB.

HRV Analysis

ECG signals of newborn infants were obtained for the HRV analysis. Electrodes were placed in a lead II position on the chest wall and connected to a monitoring system (Acknowledge III, MP150WSW BIOPAC Systems, Santa Barbara, CA, USA). All QRS complexes on ECG were automatically edited and then manually corrected by careful inspection of the RR intervals. Signals were digitalized at 500 Hz and transformed into a power spectrum by fast Fourier transformation.

The following spectral HRV parameters were obtained for analysis: standard deviation of average NN intervals (SDANN) which represents the total variability, low frequency (LF, 0.02–0.2 Hz) which represents both parasympathetic and sympathetic functions; high frequency (HF, 0.2–1 Hz) which represents parasympathetic function, and total power (TP, 0.02–1 Hz) which represents the overall autonomic nervous system function.[16–18] LF, HF, and TP were logarithmically transformed to control for skewed distributions. LF and HF were further normalized by the percentage of TP except for very low frequency (<0.02 Hz) to detect the sympathetic (LF%) and parasympathetic (HF%) influences on the HRV.

PROCEDURES

At entrance, medical records of newborn infants and their mothers were reviewed. Maternal age, parity, gestational age at birth, gender of newborn, body weight and height of newborn, and Apgar scores were all documented. Newborn infants were submitted to HRV analysis in 3 days postpartum. All the tests were performed in the baby room. The room temperature was maintained to 22–26 °C. Infants were placed in a supine position and wrapped in a blanket. ECG signals were recorded during a daytime nap after feeding. At least 5 minutes of stationary recording was obtained for analysis.

Table 1. Characteristic Data of Newborn Infants Delivered Through Vaginal Birth or Cesarean Delivery

Variable	Vaginal Birth (n = 80)	Cesarean Delivery (n = 83)
Maternal age (year)	31.5 ± 4.1	34.2 ± 4.4[a]
Parity (n)	1.7 ± 0.9	1.6 ± 0.9
Gestational age at birth (weeks)	39.1 ± 1.1	38.4 ± 1.0
Gender of newborn (M/F)	38/42	42/41
Body length of newborn (cm)	50.1 ± 1.6	50.2 ± 1.5
Body weight of newborn (g)	3146 ± 366	3118 ± 343
1-minute Apgar score	9.2 ± 0.5	9.0 ± 0.6[a]
5-minutes Apgar score	9.9 ± 0.3	9.8 ± 0.4[a]

[a]$P < 0.05$.

Table 2. Heart Rate Variability of Newborn Infants Delivered Through Vaginal Birth or Cesarean Delivery

HRV	Vaginal Birth (n = 80)	Cesarean Delivery (n = 83)
SDANN	44.8 ± 10.5	35.6 ± 13.0[a]
LF (ms^2)	6.7 ± 0.5	6.3 ± 1.2
HF (ms^2)	5.7 ± 1.0	4.8 ± 1.3[a]
LF%	75.8 ± 9.5	81.0 ± 10.4
HF%	23.7 ± 9.5	18.0 ± 9.8[a]
TP (ms^2)	7.4 ± 0.5	6.7 ± 0.9[a]

[a]$P < 0.05$.
SDANN = standard deviation of average NN intervals; LF = low frequency; HF = high frequency; TP = total power.

Statistics

Data were analyzed using SPSS 19.0 (SPSS, Chicago, IL, USA). All data are expressed as the number or mean ± standard deviation. An independent t-test or one-way analysis of variance (ANOVA) was used to compare differences in numeric data. Post hoc analysis was done by Benferroni test. A Chi-square test was used to compare differences in quantitative data. A P value of <0.05 was considered statistically significant.

RESULTS

HRV in Newborn Infants Delivered Through VB or CD

Characteristic data of the newborn infants in the VB group and CD group are shown in Table 1. Results showed that newborns in the VB group had lower maternal age (31.5 ± 4.1 years vs 34.2 ± 4.4 years, $P < 0.05$), and higher 1-minute Apgar (9.2 ± 0.5 vs 9.0 ± 0.6, $P < 0.05$) and 5-minutes Apgar scores (9.9 ± 0.3 vs 9.8 ± 0.4, $P < 0.05$) than those in the CD group. The parity (1.7 ± 0.9 vs 1.6 ± 0.9), gestational age at birth (39.1 ± 1.1 vs 38.4 ± 1.0), gender of newborn (38/42 vs 42/41), body length of newborn (50.1 ± 1.6 vs 50.2 ± 1.5), or body weight of newborn (3146 ± 366 vs 3118 ± 343), however, did not significantly differ between the two groups.

HRV of newborn infants was then compared between the VB and CD groups in Table 2. Results showed that SDANN (44.8 ± 10.5 vs 35.6 ± 13.0), HF (5.7 ± 1.0 vs 4.8 ± 1.3), HF% (23.7 ± 9.5 vs 18.0 ± 9.8), and TP (7.4 ± 0.5 vs 6.7 ± 0.9) of newborn infants in the VB group were significantly higher than those in the CD group. LF (6.7 ± 0.5 vs 6.3 ± 1.2) and LF% (75.8 ± 9.5 vs 81.0 ± 10.4) of the two groups were not significantly different.

HRV in Newborn Infants With Different Indications of CD

Newborn infants in the CD group were categorized as elective group, dystocia group, and NRFS group. Characteristic data of the three groups are shown in Table 3. Results showed that maternal age, parity, gestational age at birth, gender of newborn, body length of newborn, and body height of newborn did not differ among the three groups. The 1- and 5-minutes Apgar scores, however, were significantly lower in the NRFS group (8.7 ± 0.7 and 9.6 ± 0.6) than in the elective group (9.2 ± 0.5 and 9.9 ± 0.2) and dystocia groups (9.1 ± 0.7 and 9.8 ± 0.4).

HRV parameters were then compared among groups with different indications of CD in Table 4. Results showed that the NRFS group had a significantly lower SDANN (26.3 ± 8.8 vs 41.3 ± 11.8), HF (4.5 ± 0.6 vs 4.9 ± 0.9), and TP (5.9 ± 0.7 vs 7.2 ± 0.6) than those of the elective group, and a significantly lower HF (4.5 ± 0.6 vs 4.9 ± 0.8), HF% (15.7 ± 6.7 vs 19.9 ± 8.3), and TP (5.9 ± 0.7 vs 6.8 ± 0.8) than those of the dystocia group. Other differences in HRV parameters among the three groups were not significant.

Table 3. Characteristic Data of the Newborn Infants Delivered Through Cesarean Section With Different indications

Variable	Elective (n = 32)	Dystocia (n = 29)	NRFS (n = 22)
Maternal age (year)	34.8 ± 3.5	33.8 ± 4.6	34.3 ± 4.2
Parity (n)	1.8 ± 0.9	1.4 ± 0.8	1.8 ± 0.9
Gestational age at birth (week)	38.2 ± 0.7	38.6 ± 1.0	38.3 ± 1.1
Gender of newborn (M/F)	15/17	18/10	8/14
Body length of newborn (cm)	50.2 ± 1.4	50.5 ± 1.4	49.8 ± 1.6
Body weight of newborn (g)	3168 ± 347	3156 ± 338	2998 ± 328
1-minute Apgar score	9.2 ± 0.5	9.1 ± 0.7	8.7 ± 0.7[a,b]
5-minutes Apgar score	9.9 ± 0.2	9.8 ± 0.4	9.6 ± 0.6[a,b]

[a]$P < 0.05$, vs elective.
[b]$P < 0.05$, vs dystocia.
NRFS = nonreassuring fetal status.

Table 4. Heart Rate Variability of Newborn Infants Delivered Through Cesarean Section With Different Indications

Variable	Elective (n = 32)	Dystocia (n = 29)	NRFS (n = 22)
SDANN	41.3 ± 11.8	36.1 ± 13.1	26.3 ± 8.8[a]
LF (ms^2)	6.4 ± 0.4	6.3 ± 0.3	6.2 ± 0.3
HF (ms^2)	4.9 ± 0.9	4.9 ± 0.8	4.5 ± 0.6[a,b]
LF%	81.1 ± 10.4	80.5 ± 11.8	81.5 ± 7.0
HF%	17.9 ± 9.4	19.9 ± 8.3	15.7 ± 6.7[b]
TP (ms^2)	7.2 ± 0.6	6.8 ± 0.8	5.9 ± 0.7[a,b]

[a]$P < 0.05$, vs elective.
[b]$P < 0.05$, vs dystocia.
NRFS = nonreassuring fetal status; SDANN = standard deviation of average NN intervals; LF = low frequency; HF = high frequency; TP = total power.

DISCUSSION

Our novel findings showed that, newborn infants delivered through Cesarean section had lower autonomic nervous system function, which manifested mainly in the parasympathetic branch. Causes of Cesarean-associated low HRV might be multifactorial. In our series, newborn infants in the CD group had lower Apgar scores. The 1-minute Apgar score was reported to correlate with total serum calcium,[19] which influences the membrane potential of neuronal cells and thus alters their conductivity. Low Apgar scores, acting through a pathway other than birth asphyxia, were also confirmed to be a risk factor for chronic neurological disability.[20] Besides, VB help squeeze the amniotic fluid from the baby's lungs. Comparatively, babies could aspirate amniotic fluid or blood at the time of surgery. As a result, newborn infants delivered through Cesarean section have a higher risk of neonatal respiratory morbidity,[12] which has been demonstrated to associate with lower HRV.[21] Furthermore, babies born through a planned Cesarean section were suggested to receive less fetal placental perfusion than during VB.[22] However, whether hemodynamic changes due to periodic contractions of uterus during VB affect the autonomic nervous system function of newborns remains unknown.

In this study, the decreased autonomic nervous system function in newborn infants in the CD group was obvious if they had experienced NRFS during labor. NRFS-associated hypoxia and acidemia could damage the neuronal cells directly, or interfere with the cell functions through increase of capillary permeability, leakage of cytosolic enzymes, and release of oxygen-derived free radicals.[23] Lipid peroxidation products and antioxidant functions were proven to elevate in umbilical cord blood and the placenta of infants with NRFS, suggesting the destruction of membrane lipids by free radicals.[24] The physiology of abnormal fetal heart rate patterns has been well studied. During hypoxia, chemoreceptors are triggered

causing vessel constriction and hypertension. The deceleration of fetal heart rate reveals the reflex vagal response of baroreceptor to hypertension.[25] Comparatively, loss of fetal heart rate variability implies the depression of the central nervous system secondary to hypoxia,[26] and fetal heart variations demonstrated to be the most extensively studied parameter that correlates with the presence of metabolic acidosis.[27] We suggested that the decrease of HRV in neonates could be the extension of abnormal heart rate patterns, but their causal relationship need to be further elucidated.

The normal human fetus has compensatory mechanisms that allow it to withstand severe acidosis and hypoxia for short periods of times.[4] As a result, it is not surprising that the correlation between NRFS and cerebral palsy is poor,[28] and the rate of cerebral palsy remains unchanged even with the widespread use of EFM.[29] Many abnormal EFM patterns are associated with a normal cord pH, and only a small proportion of neonates who have the dramatic EFM patterns are born acidotic.[30] The decreased autonomic nervous system function in neonate infants who had NRFS may be a temporal response to intrapartum hypoxia. The clinical significance of changes in postnatal HRV requires further evaluation.

There are some limitations of this study. First, although EFM is one of the most widely accepted methods of assessing fetal wellbeing, the interpretation of FHR tracings is subjective and not very reproducible.[31] Second, severely compromised neonates were either intubated or given medications, and thus could not be included in this study. Third, due to the lack of long-term follow-up data, it is not known whether a decrease of HRV in newborns is associated with later neurological outcomes.

We concluded that newborn infants delivered through Cesarean section had lower HRV, especially those who experienced NRFS during labor. The long-term effects of changes of HRV in neonates require further evaluation.

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