Fetal Heart Rate Patterns in Neonatal Hypoxic-Ischemic Encephalopathy: Relationship with Early Cerebral Activity and Neurodevelopmental Outcome

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ABSTRACT

Despite widespread use of fetal heart rate monitoring, the timing of injury in hypoxic-ischemic encephalopathy (HIE) remains unclear. Our aim was to examine fetal heart rate patterns during labor in infants with clinical and electroencephalographic (EEG) evidence of HIE and to relate these findings to neurodevelopmental outcome. Timing of onset of pathological cardiotocographs (CTGs) was determined in each case by two blinded reviewers and related to EEG grade at birth and neurological outcome at 24 months. CTGs were available in 35 infants with HIE (17 mild, 12 moderate, 6 severe on EEG). Admission CTGs were normal in 24/35 (69%), suspicious in 8/35 (23%), and pathological in 3/35 (8%). All CTGs developed nonreassuring features prior to delivery. Three patterns of fetal heart rate abnormalities were seen: group 1, abnormal CTGs on admission in 11/35 (31%); group 2, normal CTGs on admission with gradual deterioration to pathological in 20/35 cases (57%); and group 3, normal CTGs on admission with acute sentinel events in 4/35 (11.5%). The median (interquartile range) duration between the development of pathological CTGs and delivery was 145 (81, 221) minutes in group 2 and 22 (12, 28) minutes in group 3. There was no correlation between duration of pathological CTG trace and grade of encephalopathy ($R = 0.09$, $p = 0.63$) or neurological outcome ($p = 0.75$). However, the grade of encephalopathy was significantly worse in group 3 ($p = 0.001$), with a trend to worse outcomes. The majority of infants with HIE have normal CTG traces on admission but develop pathological CTG patterns within hours of delivery. More severe encephalopathy was associated with normal admission CTG and acute sentinel events shortly before delivery.

KEYWORDS: Neonatal, hypoxic-ischemic encephalopathy, electroencephalography, cardiotocograph, neurological outcome

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Hypoxic-ischemic encephalopathy (HIE) is an evolving pattern of neurological dysfunction following perinatal hypoxic-ischemic injury. It continues to affect 3 to 5 per 1000 live births with an outcome that varies considerably—from normal to severe neurological disability or death.[1] Despite almost universal monitoring of fetal heart rate (FHR) patterns prior to and during labor, their benefit in predicting a compromised infant is controversial.[2] Retrospective reviews of cardiotocographs (CTGs) in neurologically abnormal infants have related characteristic patterns to outcome; however, the false-positive rate of an abnormal CTG is high.[3,4] In contrast, a normal, reactive CTG is highly predictive of a normal outcome.[5,6]

Many studies examining FHR changes and outcome have used cerebral palsy as a surrogate outcome measure, despite the fact that the origins of cerebral palsy are varied, and often idiopathic.[3,7] More recent research has reported the patterns of CTG abnormalities with clinical neonatal encephalopathy.[8] However, criteria used to diagnose HIE vary, with considerable overlap with other causes of neonatal encephalopathy. Electroencephalography (EEG) provides an accurate assessment of the degree of encephalopathy and reliable prognosis.[9,10]

Although many infants with HIE are defined by the presence of a pathological CTG pattern at delivery, the time at which this abnormal CTG pattern develops has not been previously documented. The aim of this study was to chart the development of pathological CTG changes prior to delivery in infants with EEG-confirmed HIE. We wished to establish the time before delivery at which CTG traces become pathological and to correlate these findings with EEG grade of encephalopathy and neurological outcome at 24 months.

METHODS

This was a prospective study in a large maternity service (5500 deliveries per annum) performed from May 2003 to October 2005 examining early continuous EEGs in HIE. All infants who fulfilled the criteria for HIE were recruited as soon as possible after delivery. This was defined as having two or more of the following: Apgar score <5 at 5 minutes, initial pH <7.1, lactate >7 mmol/L, abnormal neurology, or seizures. Infants who met the initial criteria were examined using a standardized method of neonatal neurological assessment, the Amiel-Tison method.[11] Parents were approached following assessment and informed consent was obtained.

EEG Analysis

Silver-chloride EEG electrodes were applied to the scalp at F3, F4, C3, C4, T3, T4, O1, O2, and CZ (using the international 10 to 20 system of electrode placement, modified for neonates). The VIASYS NicOne EEG Monitor (Viasys Healthcare, Cardinal Health, Warwick, UK) was used to record continuous video EEG for durations of 24 to 72 hours. Recordings were commenced as soon as possible after birth, generally within 6 hours. Video EEG was analyzed by an experienced neonatal electroencephalographer. The background activity of the EEG was graded at 24 hours after birth as mild, moderate, or severe according to a standardized grading system.[12] The onset of electrographic seizures (if present) was noted in each case.

CTG Analysis

CTG recordings were photocopied or scanned from the maternal notes, along with maternal and obstetric details. CTGs were analyzed separately by two experienced obstetricians. The obstetricians were blinded to the neonatal outcome and EEG findings. To help the process of blinding, the CTG recordings of 20 control infants with uncomplicated deliveries, normal Apgar scores, and uneventful neonatal courses were included in the CTG analysis group. The CTG findings of these control infants were not used for comparison with our cohort group, merely to aid the blinding process. CTGs were reviewed according to the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines (Table 1), and admission CTGs were graded as normal, suspicious, or pathological. If the admission CTG was normal, the time of deterioration of the CTG to suspicious and pathological grades were determined. In cases where our observers differed in opinion, a third obstetric opinion was used to reach consensus.

Using the above analysis, the CTGs were divided into three groups: group 1, those who had abnormal CTGs on admission (either suspicious or pathological); group 2, those who were normal on admission who then deteriorated gradually from normal through suspicious to pathological grades; and group 3 those who were normal on admission and then underwent an abrupt deterioration (due to an acute sentinel event). This was defined as a normal reactive CTG, which deteriorated acutely to pathological and/or a supporting diagnosis of an obstetric emergency such as placental abruption or uterine rupture leading to a sudden bradycardia that continued up to delivery.

Neurological Assessment and Follow-up

Infants were examined in the newborn period using a standardized neurological assessment,[11] and clinical Sarnat scoring was performed at 24 hours.[13] Developmental follow-up was assessed using the Griffiths Scales of Mental Development at 24 months.[14] A neurological

Table 1 CTG Classification

CTG Classification				
Normal	A CTG where *all four* features fall into the reassuring category			
Suspicious	A CTG whose features fall into *one* of the non-reassuring categories and the remainder of the features are reassuring			
Pathological	A CTG whose features fall into *two or more* non-reassuring categories or *one or more* abnormal categories			
Fetal Heart-Rate Feature Classification				
	Baseline (bpm)	**Variability (bpm)**	**Decelerations**	**Accelerations**
Reassuring	110–160	≥5	None	Present
Nonreassuring	100–109 161–180	<5 for >40 but <90 min	Early deceleration Variable deceleration Single prolonged deceleration up to 3 min	*
Abnormal	<100 >180 Sinusoidal pattern for ≥10 min	<5 for ≥90 min	Atypical variable decelerations Late decelerations Single prolonged deceleration greater than 3 min	

*The absence of accelerations with an otherwise normal CTG is of uncertain significance.
CTG, cardiotocograph; bpm, beats per minute.
Modified from the guidelines of the Royal College of Obstetricians and Gynaecologists, UK.

assessment of motor function was performed at the same time. An abnormal outcome was defined as a general quotient less than 87, significant motor dysfunction, or death.

Statistical Analysis

The median (interquartile range) time in minutes before delivery from the development of a pathological CTG pattern was determined in each group. The differences between the groups in terms of grades of encephalopathy and outcome were determined using Kruskal-Wallis test. The correlations between time of onset of pathological CTG and grade of encephalopathy and outcome were determined using Spearman rank sum test. The occurrence of individual CTG features in the two outcome groups (neurologically normal versus abnormal) was compared using the Kruskal-Wallis test. A p value of <0.05 was considered to be statistically significant.

RESULTS

During the recruitment period, 50 infants were born with clinical and electroencephalographic HIE. In six infants, prenatal fetal heart monitoring was unavailable: three were planned home deliveries, one was born en route to hospital, and two were external transfers. In addition, nine CTG recordings were inadequate (too short [<20 minutes] or of poor quality) and were excluded from analysis.

The 35 infants with both prenatal FHR monitoring and postnatal EEG monitoring were the focus of this study. There were 19 male and 16 female infants (34 singletons, one twin pregnancy) with an overall mean (standard deviation [SD]) birth weight of 3330 (625) grams and a mean (SD) gestation of 40.1 (1.6) weeks. Their delivery details, EEG grades, and outcomes are outlined in Table 2. Mean (SD) maternal age was 29.5 (6.4) years. The majority (27/35; 77%) of mothers were nulliparous. Fetal scalp blood sampling and postnatal cord blood sampling were not routinely performed in our institution at the time of this study. First blood gases (arterial and capillary) within 30 minutes of birth are recorded in Table 2. Electrographic encephalopathy grades were mild in 17 (49%), moderate in 12 (34%), and severe in 6 (17%) infants.

CTG Analysis

PATTERNS OF CTG DETERIATION

Group 1 (Abnormal CTG on Admission) In 11/35 (31%) cases, CTGs were abnormal on admission to hospital. Of these, 3/35 (8%) were pathological and 8/35 (23%) were suspicious. The three pathological cases remained so until delivery (50, 150, and 690 minutes later). The eight suspicious CTGs gradually deteriorated to become pathological in all cases. The median (interquartile range) time prior to delivery at which they became pathological was 88.5 (65, 322) minutes.

Group 2 (Normal CTG on Admission with Gradual Deterioration) In 20/35 cases (57%), CTG traces were normal on admission and gradually deteriorated to become pathological prior to delivery. The median (interquartile range) duration between becoming pathological and delivery was 145 (81, 221) minutes in this group.

Table 2 Delivery and Outcome Details of Individual Cases

Study No.	Mode of Delivery	First pH	Apgar 5	EEG Grade	Admission CTG	Duration	Outcome
1	EMCS	6.9	8	1	Abnormal		N
2	V	7	8	2	Abnormal		N
3	EMCS	7.13	10	1	S	60	N
4	EMCS	7.09	6	1	S	90	N
5	V	7.2	6	2	S	80	N
6	EMCS	6.8	5	2	S	388	N
7	NVD	7.1	8	2	S	325	N
8	EMCS	7.18	6	2	Abnormal		ABN
9	F	6.5	5	3	S	315	Died
10	V	6.78	1	3	S	87	Died
11	F	7.06	7	3	S	60	ABN
12	V	6.99	7	1	N	170	†
13	EMCS	7.16	7	1	N	37	N
14	F	6.8	5	1	N	45	N
15	V	7.01	7	1	N	60	N
16	V	6.95	7	1	N	80	N
17	V	7.01	5	1	N	85	N
18	V+F	7.2	9	1	N	90	N
19	EMCS	6.7	5	1	N	230	N
20	EMCS	7.13	6	1	N	240	N
21	EMCS	7.04	7	1	N	250	N
22	EMCS	7.05	5	1	N	285	N
23	NVD	6.8	6	1	N	150*	N
24	V+F	7.24	9	2	N	60	N
25	EMCS	6.9	8	2	N	195	N
26	NVD	7.17	7	2	N	300	ABN
27	V	6.99	4	1	N	90	ABN
28	EMCS	6.95	6	1	N	150	ABN
29	EMCS	7.17	9	2	N	120	ABN
30	V	7.04	7	2	N	140	ABN
31	V	7.16	8	2	N	195	ABN
32	EMCS	6.8	3	2	N	23	N
33	NVD	6.72	3	3	N	20	ABN
34	NVD	7.04	2	3	N	30	ABN
35	F	7.19	3	3	N	10	Died

*Cases 23 did not progress to pathological CTG, time shown is time of development of suspicious features.
†Infant with congenital diaphragmatic hernia.
EEG, electroencephalogram; EMCS, emergency caesarean section; V, vacuum extraction; F, forceps extraction; NVD, normal vaginal delivery; pH, first blood sample from infant, within 30 minutes of delivery; CTG, cardiotocograph; N, normal; ABN, abnormal; P, pathological; S, suspicious CTG. EEG grade 1 = mild, 2 = moderate, 3 = severe.

Group 3 (Normal CTG on Admission with Acute Sentinel Events) Of the total group, 4/35 (11.5%) underwent acute sentinel events (one uterine rupture, one cord prolapse [in a second twin], and two acute bradycardias 20 and 30 minutes prior to delivery). The median (interquartile range) duration between the acute event and delivery in this group was 22 (12, 28) minutes.

In the 9/50 infants with CTG recordings that were too short or of poor quality, five had mild grade of EEG encephalopathy and four were moderate. Abnormal outcomes were seen in 2/9 infants.

NEUROLOGICAL FOLLOW-UP

All 35 children had neurological follow up to 18 to 24 months of age. Of these, 34/35 were followed to 24 months, and one was seen to 18 months of age. One child was excluded as he required surgical correction of a congenital diaphragmatic hernia, which is in itself associated with an increased risk of development delay. Due to this uncertainty, his CTG was excluded from analysis of outcome.

Of the remaining children, 21/34 (62%) were normal, 10/34 (29%) were neurologically abnormal,

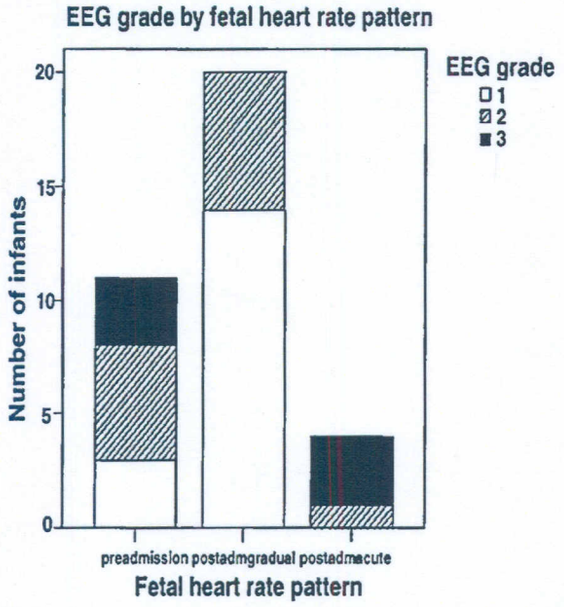

Figure 1 Electroencephalographic grades seen in each of the three fetal heart rate groups: preadmission, postadmission with gradual deterioration, postadmission with acute deterioration. Electroencephalogram grades: 1 = mild, 2 = moderate, 3 = acute.

and three died. The three deaths occurred in infants who were severely abnormal neurologically: one in the first week of life following withdrawal of ventilatory support and the others at 4 and 24 months of age, respectively. Of the 10 surviving, neurologically abnormal children, one has spastic quadriplegia and severe intellectual deficit; one has dense hemiplegia and global developmental delay; two display hemiplegia alone; one has mild diplegia; three have global developmental delay; one has isolated speech delay; and one has isolated motor delay without evidence of cerebral palsy.

The worst grades of encephalopathy were seen with CTG patterns 1 and 3 (preadmission and postadmission acute). There was a significant difference across the groups ($p = 0.001$). This is displayed visually in Fig. 1. However, this did not translate into a significant difference in outcome ($p = 0.118$). The duration of pathological CTG (minutes) prior to delivery did not correlate with EEG grade or outcome ($p = 0.116$, $p = 0.64$, respectively).

The admission CTG grade, the individual CTG features during labor, and individual outcomes are displayed on Table 3. No significant correlation was found between any individual CTG feature and outcome.

SEIZURE ACTIVITY

Of the 35 infants, eight had electrographic seizure activity. The time interval from onset of pathological CTG to onset of seizures following birth is displayed in Fig. 2. The median duration (range) from onset of pathological CTG to first seizures was 17.5 (10.3 to 23) hours.

DISCUSSION

We have shown that the many infants who develop HIE have entered labor with a normal CTG. During the course of labor, reassuring FHR responses were lost, and suspicious or pathological CTG patterns developed. The median time of this development, and hence an estimate of the time of onset of fetal distress, was ~90 minutes prior to delivery. This is consistent with the evolving pattern of EEG abnormalities seen in these infants and magnetic resonance imaging studies indicating acute injury in most cases of neonatal encephalopathy.[10,15]

Similar to limited previous studies, we saw three distinct patterns.[8,16] We also found that the worst outcomes were seen in those infants with either preadmission injuries or acute sentinel events. In both patterns, obstetric intervention may not be possible or beneficial. Our findings confirmed those of Westgate et al's, that in a significant proportion of cases CTG recordings were too short or of poor quality.[8]

Previous attempts to estimate timing of injury have been based on retrospective reviews of birth histories of children with cerebral palsy, limited to spastic quadriplegia.[3] Studies examining the onset of CTG abnormalities have focused on infants with severe neurological long-term deficits.[5,16,17] In our study, although all infants had clinical and EEG evidence of HIE, only three went on to have spastic quadriplegia (and one died in the neonatal period). Many displayed mild to moderate disability, which can still be linked to their early encephalopathy. And we can expect even more of these children to progress to subtle neurological deficits with learning difficulty at school age.[18] We cannot limit our outcome examination to just those infants displaying severe motor disability. The advantage of our study is that it is a prospective examination of all grades of HIE—mild, moderate, and severe. Examination of all cases of perinatal asphyxia, not just those with severe spastic quadriplegia, will allow us to gain a clearer picture of the timing and mechanism of hypoxia-ischemic injury.[19]

The estimated time between onset of pathological CTG and delivery was not associated with the degree of encephalopathy. In fact, there was a trend toward shorter times in infants with severe encephalopathy. Infants with acute sentinel events had the worst encephalopathy. This suggests that the mechanism of insult may be as important as the timing in determining the extent of the cerebral insult. We know that different patterns of insult produce

Table 3 Admission and Labor CTG Features in Individual Cases

Study No.	Adm CTG	Fetal Heart Rate Prior to Delivery	Acute Event	EEG Grade	Outcome at 24 mo
1	P	Bradycardia, reduced variability	No	1	N
2	P	Tachycardia, reduced variability, late decelerations	No	2	N
3	S	Tachycardia, reduced variability, variable decelerations	No	1	N
4	S	Tachycardia, late decelerations	No	1	N
5	S	Tachycardia, early decelerations	No	2	N
6	S	Tachycardia, variable decelerations	No	2	N
7	S	Reduced variability, variable decelerations	No	2	ABN
8	P	Reduced variability, variable decelerations	No	2	N
9	S	Variable decelerations	No	3	Died
10	S	Reduced variability, late decelerations	No	3	Died
11	S	Bradycardia, reduced variability, early decelerations	No	3	ABN
12	N	Bradycardia	No	1	*
13	N	Reduced variability, variable decelerations	No	1	N
14	N	Tachycardia, reduced variability	No	1	N
15	N	Tachycardia, variable decelerations	No	1	N
16	N	Late decelerations	No	1	N
17	N	Late decelerations	No	1	N
18	N	Reduced variability, late decelerations	No	1	N
19	N	Tachycardia, variable decelerations	No	1	N
20	N	Tachycardia, reduced variability, variable decelerations	No	1	N
21	N	Tachycardia, variable decelerations	No	1	N
22	N	Tachycardia, reduced variability	No	1	N
23	N	Early decelerations	No	1	N
24	N	Tachycardia, reduced variability	No	2	N
25	N	Tachycardia, variable decelerations	No	2	N
26	N	Tachycardia, reduced variability, early decelerations	No	2	ABN
27	N	Tachycardia, late decelerations	No	1	N
28	N	Tachycardia, reduced variability, variable decelerations	No	1	N
29	N	Tachycardia, reduced variability, variable decelerations	No	2	ABN
30	N	Late decelerations	No	2	ABN
31	N	Tachycardia, reduced variability	No	2	ABN
32	N	Bradycardia, reduced variability	Uterine rupture	2	N
33	N	Bradycardia	Acute bradycardia	2	ABN
34	N	Bradycardia, absent variability	True cord knot	3	ABN
35	N	Tachycardia	Cord prolapse	3	Died

*Case 12: infant with congenital diaphragmatic hernia whose outcome was excluded from analysis.
CTG, cardiotocograph; Adm, admission; N, normal; S, suspicious; P, pathological; ABN, abnormal neurological outcome at 24 months.

different injuries.[20] Frequently, the most severe injury may occur following almost acute near-total asphyxia where the deep brain structures of the brain are the most severely affected.[21,22]

Although the CTG features seen were as expected in infants undergoing hypoxic-ischemic stress,[23,24] no features in particular were associated with a worse outcome. Unfortunately, we did not have access to fetal scalp or cord blood samples at the time of this study. This would have improved our ability to plot the development of fetal compromise. The first blood gas sampling was done in the neonatal intensive care unit, within 30 minutes of birth. The effect of neonatal resuscitation will therefore have been incorporated into these results.

The effect of the antenatal condition of the infant will also have a role to play. Factors that have been found to be associated with neonatal encephalopathy include maternal thyroid disease, socioeconomic status, antepartum hemorrhage, and preeclampsia.[25] These factors will affect the infant's ability to deal with the stress of labor. But these factors alone are not enough. Neonatal encephalopathy rarely occurs in infants delivered by prelabor elective caesarean section.[26]

The narrow window of 90 minutes prior to delivery could theoretically offer an opportunity for

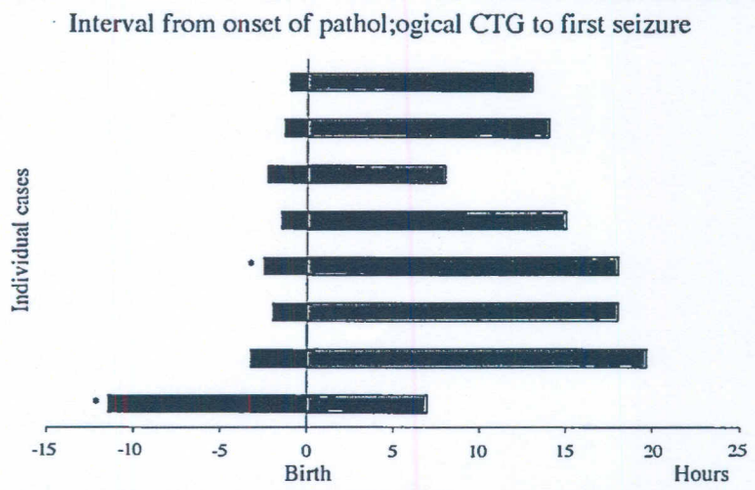

Figure 2 Interval (hours) from estimated injury to onset of first seizure in the eight infants with clinical and electrographic seizures. *Cases 1 and 18 had abnormal cardiotocographs (CTGs) on admission, so interval may have been longer than that illustrated.

intensive monitoring and intervention. However, our current screening methods fall far short of the mark. CTG is too sensitive and lacks specificity.[4] Acidosis takes time to develop. The worst grades of encephalopathy were seen in the two groups that are most difficult to prevent: the preadmission injury and the sudden sentinel event.

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