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Physiological CTG categorisation in types of hypoxia compared with MRI and neurodevelopmental outcome in infants with HIE.

Keywords: Cardiotocography, electronic fetal heart rate monitoring, magnetic resonance imaging, neurodevelopmental outcome, neonatal encephalopathy, physiological CTG.

Abstract:

Background Commonly used methods of CTG classification do not reliably predict neonatal hypoxic-ischemic encephalopathy (HIE).

Objective: To examine whether a relationship exists between the types of hypoxia as identified on the cardiotocograph using a novel physiology based CTG classification and patterns of injury on neonatal cerebral MRI and later neurodevelopmental outcomes.

Study design: A retrospective study of term-born infants admitted to four neonatal units with HIE as part of a brain injury biomarkers study between January 2014 and December 2015. Intrapartum CTG traces were analysed by two obstetricians trained in a novel physiology based CTG classification, blind to neonatal outcomes. Neonatal cerebral MR images were assessed independently by a neuroradiologist and an expert neonatologist. CTG traces were classified into types of hypoxia and allocated to groups; 1) chronic hypoxia or antepartum injury; 2) gradually evolving or subacute hypoxia and 3) acute hypoxia.

Results: Of 106 infants recruited to the study, records were available for 58 cases. Of these, CTGs were available for 37. All 37 had abnormal CTGs. Twenty-four infants, all of whom had received therapeutic hypothermia had cerebral MRI. Fourteen of the 24 (58%) infants had abnormal MRI. In group 1 (chronic hypoxia/ antenatal injury), total brain injury was most predominant (4/6 infants). Group 2 (gradually evolving/ subacute hypoxia) was associated with peripheral brain injury (5/5 infants). Group 3 (acute hypoxia) was associated with basal-ganglia thalamic injury pattern (3/3 infants). Later neurodevelopmental outcomes were available for 35 cases. Infants suspected to have pre-labour injury on CTG (group 1) had a higher proportion of adverse neurodevelopmental outcome (4/10, 40%) compared to groups 2 and 3 (4/25, 16%).

Conclusion: Using this novel physiology based CTG classification, we demonstrate an association between types of hypoxia observed on the CTG and MRI patterns of hypoxic brain injury. Infants with CTG trace suggestive of chronic hypoxia or other antenatal injuries were overrepresented in this cohort and were also more likely to have a poor neurodevelopmental outcome.

Introduction:

Hypoxic ischemic encephalopathy (HIE) is the largest contributor to term neonatal brain injury in the Western world with an annual incidence of 2.4-2.8 per 1000 live births for moderate and severe cases.[1] Up to 45% of newborns with HIE who are treated with mild therapeutic hypothermia, now an established standard of care[2,3] have been shown to suffer substantial disability or death.[4,5]

Cardiotocography (CTG) was introduced in clinical practice with the aim of preventing HIE, however its value has been an ongoing topic of debate. A Cochrane review of trials evaluating the efficacy and safety of the intrapartum CTG showed that although the use of CTG is associated with a reduction in neonatal seizures it does not prevent perinatal death or cerebral palsy.[6] Furthermore, CTG monitoring has been associated with rising caesarean section rates which are independently associated with maternal risks.[6]

A key issue with the use of CTG is interpretation. Several reports have suggested CTG misinterpretation as the main contributory cause in preventable cases of HIE and perinatal deaths.[7,8] There are different guidelines worldwide for CTG interpretation.[9] There is not only substantial inter-observer disagreement using individual guidelines but also poor agreement when comparison is made across different guidelines.[10,11] Furthermore, some experts argue that looking at CTG on the basis of pattern recognition alone with emphasis on FHR decelerations results in unnecessary interventions for non-acidotic babies who mount normal responses to hypoxia and has no correlation with neonatal outcomes.[12,13]

Physiological CTG classification in types of hypoxia, a novel approach to CTG interpretation requires assessment of fetal heart rate (FHR) features in a physiological context where it forms part of a dynamically evolving FHR trace, that is representative of fetal cardiovascular response to stress.[13-15] Emphasis is placed on identifying an already compromised fetus at the start of labour which has signs of chronic hypoxia or antepartum injury before labour or early on in the intrapartum CTG.[14,16] Focus is then shifted to evaluating normal fetal physiological responses to the hypoxic stresses of labour. These fetal responses can be challenged as a result of maternal and fetal conditions (intrauterine growth restriction (IUGR), diabetes and hypertension), interventions in labour such as the use of oxytocin or presence of a sentinel event, which can impact the intensity and duration of hypoxia experienced by the fetus and result in harm.[15,17] The fetal response will vary with the duration and intensity of the hypoxic stress. The CTG is classified as representing gradually evolving, subacute and acute hypoxia. The recognition of types of hypoxia alongside any signs of decompensation will allow for timely intervention to relieve stresses on the fetus and or expedite delivery.[14,15]

The aim of this study is to examine whether categories of postulated hypoxia as identified on the CTG using this novel physiology-based approach to CTG classification are associated with patterns of cerebral injury on neonatal MRI as well as neurodevelopmental outcome, hence reflecting severity of HIE.

Materials and methods:

Term infants born between January 2014 and December 2015 diagnosed with HIE admitted to four Neonatal Intensive Care Units (NICUs)– namely the Royal London Hospital,

Homerton University Hospital, Ashford and St Peter's Hospital and Southampton University Hospital, were recruited as part of the prospective observational Brain Injury Biomarkers in Newborns Study (BIBiNS).[18-20] Research and ethics approval was obtained (REC 13/LO/17380) with consent taken from the parents of infants involved.

Patients:

The diagnosis of HIE was made on a clinical basis by the attending consultant neonatologist and standard criteria were used to treat babies with mild therapeutic hypothermia appropriately. [21] Exclusion from study included infants born <36 weeks' gestation, infants with inborn errors of metabolism, congenital structural brain abnormality or a genetic mutation. For this particular study, infants without a CTG trace prior to delivery and multiple pregnancies were also excluded. Antenatal data were obtained from the maternal notes which aided the analysis of CTG traces. HIE grade or severity scores were assigned as part of selecting babies for mild therapeutic hypothermia using the UK TOBY Cooling Register criteria.[21]

CTG analysis:

Intrapartum CTG traces were interpreted by two obstetricians (SP, AZ) independently who were blind to APGAR scores, pH and base excess values, severity of HIE, MRI findings and infant neurodevelopmental outcomes. The whole duration of the CTG trace was made available for interpretation although in some cases the CTG trace was only available for the late stages of labour.

The CTG is classified as showing no signs of hypoxia if the baseline is stable, the variability is normal, cycling is present and there are no repetitive decelerations. The classification into types of hypoxia was used as described in Table 1 which is based on Physiological CTG guidelines. When more than one type of hypoxia was identified in the same case the group allocation was as follows:

1. All cases with reduced or sinusoidal variability and no cycling prior to or at early stages of labour were allocated to group 1- chronic hypoxia or other antenatal injury.
2. When the predominant pattern of hypoxic stress was gradually evolving hypoxia (GEH) or subacute hypoxia the case was allocated to group 2. This represents the cases where fetal response is not compromised by antenatal events and at the same time there are no acute or intrapartum accidents; the CTG trace starts with normal baseline and normal variability, decelerations appear followed by an increase in baseline secondary to release of catecholamines – a compensated state. If the hypoxic stress continues beyond the capacity of the fetus to compensate, it is followed by changes in variability (GEH decompensated) or reduced time at the baseline (subacute hypoxia). In the absence of intervention, an end stage follows with unstable baseline and terminal bradycardia.
3. If the main feature on the CTG trace was a prolonged deceleration prior to delivery (acute hypoxia) the case was allocated to group 3. These are typically the cases where a sentinel event occurred (uterine rupture, placental abruption, cord prolapse or shoulder dystocia).

The population of infants with abnormal CTGs was therefore divided into 3 groups according to CTG classification: group 1- chronic hypoxia or other antenatal injury, group 2- gradually evolving and subacute hypoxia and group 3 – acute hypoxia. Additional features, such as

the presence of chorioamnionitis, that may have affected the characteristics of the CTG traces, were also noted. CTG findings suggestive of chorioamnionitis on the CTG are described as an increase in baseline fetal heart rate not preceded by decelerations and absence of cycling.[22,23]

Cerebral MRI and neurodevelopmental outcomes:

Infants had conventional T1 and T2 weighted MRI sequences at 1.5 or 3.0 Tesla at local centers as per local practice as previously described[20] using the scoring system described by Rutherford et al.[24] MR images were also grouped according to the injury pattern as well as severity: total brain injury (≥3 regions involved including BGT, PLIC or WM), peripheral injury patterns (WM and cortical involvement) and finally the basal-ganglia thalami injury pattern (BGT with associated PLIC injury).[25]

Neurodevelopmental follow-up assessments were conducted by local multidisciplinary teams as per local clinical protocols as previously described.[20,26]

Statistical analysis:

IBM SPSS Statistics 26 was used to carry out statistical comparisons in perinatal data amongst the cohort of cases who received therapeutic hypothermia and those with mild HIE who did not. The Fisher's Exact test was used for categorical data and the Mann Whitney U test for continuous variables where $p<0.05$ indicated significance. The remaining data were assessed using descriptive statistics. Data were summarized descriptively for the total cohort and between the different CTG groups. For continuous variables the median and range are presented and for categorical variables the number (percentage) is given.

Results:

Cohort:

During the study period, 174 newborns received therapeutic hypothermia treatment across the four centres. Of the 106 babies recruited (83 cooled and 23 with mild HIE) 58 antenatal records were available for review. Thirty-seven of these infants had continuous fetal monitoring for at least 15 min prior to delivery with a good quality CTG and were included in our study. In the remaining 21 cases CTG analysis was not possible: 9 had intermittent auscultation monitoring performed instead of CTG in a low risk setting, 6 had a very short or poor-quality CTG traces, the CTG was not available in 4 cases and 2 infants were delivered by elective caesarean section.

Baseline neonatal characteristics:

Perinatal characteristics were compared amongst infants who had mild HIE and those who received therapeutic hypothermia and is outlined in Table A.1. Perinatal characteristics for each case has been outlined in Table A.2. Of 37 babies, 24 received mild therapeutic hypothermia and had significantly lower Apgar scores, with a higher proportion requiring respiratory support and having seizures. Eighteen infants had emergency caesarean sections, 13 were born by instrumental assisted delivery (vacuum or forceps) and 6 infants were born by normal vaginal deliveries.

CTG analysis and grouping:

CTG was available for 37 infants with a median duration of 4.2 hours (range, 0.3-27.3). The median duration of CTG in each group is given in Table A.3. All 37 cases had abnormal CTGs. Initial agreement between assessors for group allocation was reached in 78% (n=29) of

cases and after discussion consensus was reached in the remaining 8 cases. The majority of the cases (n=18) were allocated to group 2 (gradually evolving/sub-acute hypoxia), followed by 10 cases in group 1 (chronic hypoxia), and 9 cases allocated to group 3 (acute hypoxia). Figure 1 depicts examples of CTG traces of infants in this cohort allocated to each group. Table A.4 details each case, the types of hypoxia identified alongside the encephalopathy scores, MRI injury patterns and neurodevelopmental outcomes available for each infant in our cohort.

MRI findings:

Twenty-four of the 37 babies had cerebral MRI imaging (median age at imaging 9.5 days (range, 6-60)). Table A.5 details the component cerebral MR injury scores and their associated injury patterns.

Cerebral MRI injury pattern related to CTG groups:

Of the 24 newborns who had cerebral MR imaging, 14 were abnormal. Out of infants with injury on MRI (14/24) the predominant injury patterns seen in group 1 (chronic hypoxia) was total brain injury (n=4/6), in group 2 (subacute hypoxia) was the peripheral brain injury (n=5/5) and finally in group 3 (acute hypoxia), basal-ganglia thalamic injury was the brain injury pattern seen (n=3/3).

Neurodevelopmental outcomes related to CTG groups:

Neurodevelopmental follow up was available for 35 children at a median age of 2.8 years (n= 30, range, 0.4-3.9) (Table A.6). Twenty-one children had Bayley Scales of Infant Development-III (BSID-III) assessment, 13 children were assigned outcomes based on clinical

review and one had Ages and Stages-III questionnaire (ASQ-3) assessment. Twenty-seven children had normal and eight had adverse outcomes. All adverse outcomes were determined using BSID-III assessment. Three children in group 1 had cerebral palsy and one child in group 3. Infants suspected to have pre-labour injury (group 1) had a higher proportion of adverse neurodevelopmental outcome (4/10, 40%) compared to groups 2 and 3 (4/25, 16%).

Comment

Principal findings

This study shows a clear association between types of hypoxia using physiological CTG guidelines and patterns of brain injury on MRI consistent with HIE. In babies with abnormal cerebral MR imaging all those with a total brain injury pattern had a CTG consistent with chronic hypoxia or antenatal injury, two thirds of those with peripheral pattern of brain injury had a gradually evolving or subacute hypoxia CTG category and all of those with a basal ganglia-thalamus (BGT) injury pattern were associated with an acute hypoxia CTG pattern. Adverse neurodevelopmental outcome was more common in children who had had CTG consistent with chronic hypoxia and other antenatal events compared with infants who had CTGs consistent with features of intrapartum hypoxia. In addition, infants with a chronic hypoxia/antenatal injury pattern represented 27% of our cohort.

Results in the context of what is known:

To our knowledge this is the first study to demonstrate worse neurodevelopmental outcomes associated with CTG features suggestive of chronic hypoxia/ antenatal injury compared with intrapartum hypoxia. In unselected populations, the incidence of abnormal

CTG as an admission test is thought to be only 3-5%.[27] However other studies suggested that approximately one-third of the infants with neonatal encephalopathy had an abnormal CTG at the beginning of labour[28,29] similar to our findings.

With regards to MRI outcomes, a small single centre cohort study has also demonstrated an association between gradually evolving or subacute hypoxia on the CTG with 'watershed injury' on MRI scan in infants with HIE.[30] Findings on the CTG and cerebral MRI are the result of the duration and severity of hypoxic stress (Table 2). Acute hypoxia on the CTG is characterized by a sudden drop in the fetal heart rate lasting more than 5 minutes and is associated with an acute, short lasting but intense hypoxic stress. There is experimental evidence from classic studies in primates that the pattern of brain injury noted depends on the duration and severity of hypoxia and acidosis.[31] It is postulated that an acute hypoxic-ischemic insult will most likely affect the BGT, a vascular region of the brain which is high in metabolic activity. In contrast, in gradually evolving and subacute hypoxia the insult may be less intense but prolonged through the labour allowing for time for shunting of blood from the more peripheral cerebral circulation and maintaining adequate perfusion to vital structures including the brain stem, BGT and the cerebellum. This may lead to ischemia affecting the peripheral subcortical white matter areas at the "watershed" borders of the circulatory supplies and hence produce a peripheral injury pattern seen on the MRI (also known as the parasagittal, watershed, or border-zone injury patterns). When the hypoxic insult is both severe and of longer duration, injury is more severe, with occasional involvement of the dorsal brainstem and entire cerebral cortex, a pattern of total brain injury. These are all patterns of injury noted on cerebral MRI of newborns after HIE.[24]

Physiology based CTG interpretation recommends a step wise approach with the first step being to exclude chronic hypoxia and other antenatal events that compromise the capacity of fetal response to the normal hypoxic stress of labour .[13,16] A CTG checklist to be used at the beginning of labour to identify the fetus not fit for labour, i.e., those with CTG patterns suggestive of chronic hypoxia and other antenatal events like anemia or infection, is recommended.[16]

In an experimental model, a weaker cardiac and vasomotor baroreflex response to acute hypotension and impaired peripheral vascular reactivity to α1-adrenergic agonists in chronically hypoxic fetus on an animal model has been demonstrated.[32] Such effects may explain the greater susceptibility of the human fetus exposed to chronic hypoxia to a second intrapartum “hit”. It also explains why we cannot apply the current commonly used methods of CTG interpretation to the fetus suffering chronic hypoxia. It is likely, that the degree of intrapartum hypoxia that a chronically hypoxic fetus can tolerate may be lower compared to the uncompromised fetus. Furthermore, the cardiovascular response captured by the CTG shows a different pattern with shallow, less pronounced decelerations or no decelerations at all.

Clinical implications:

The designation of HIE, of any severity is an important endpoint in the evaluation of obstetric care, irrespective of MRI results. The findings of our study support physiological CTG interpretation using a classification of types of hypoxia to predict neurodevelopmental outcome and MRI findings, in babies who require admission to the neonatal unit after hypoxia-ischemia. A fetus exposed to hypoxic stress of labour is not necessarily a fetus

compromised or with hypoxia of the central organs (heart, brain and adrenals). Types of hypoxia on the CTG is a classification based on fetal response to hypoxic stress depending on its duration and intensity that has the potential to inform the clinician when to intervene. Understanding of these CTG patterns is also an important consideration in the elucidation of the timing and mechanism of HIE and subsequent neurological injury which may inform the decision to use therapeutic hypothermia. One of the abiding problems of HIE and the need for therapeutic hypothermia is the understanding of the duration of hypoxia/ischemia and hence relationship to adverse neurodevelopment. In this regard CTG patterns may be of greater relevance than the cord pH. Although there is a dose-dependent relationship between the degree of acidosis and the likelihood of adverse outcome, most babies with pH < 7.0 will not develop cerebral palsy and babies with HIE can have normal pH at birth.[33] The primary aim of continuous fetal monitoring is to recognize the fetus at risk of HIE, so far the current national guidelines have failed to do this at a population level.[6]

Research implications:

Prospective trials are required to evaluate whether the physiology-based interpretation of the CTG demonstrated in this study are associated with better neonatal and neurodevelopmental outcomes. Further studies are indicated to validate the sensitivity of physiology based CTG interpretation in detecting vulnerable infants where normal and pre-term infants are included in analysis. Furthermore, given the potential usefulness of CTG traces to neonatal care we believe they should be added to every neonatal record.

Strengths and limitations:

To our knowledge, this is the first study relating categories of hypoxia identified using a physiology-based method of interpretation of the CTG with both cerebral MRI and neurodevelopment outcome. This is a multicentre study where assessors of the CTG and the neonatal outcomes assessed in a blinded fashion. The CTGs were reviewed by two independent experts blinded to neonatal outcomes but were aware that the infants were admitted to the neonatal unit with a diagnosis of HIE. The study was limited by its retrospective design. Also, CTG traces were not available for all the babies, for the entire duration of labour with only a very short trace prior to delivery in some cases. There was also limited clinical information e.g., on the use of prostaglandins for induction of labour and the stage of labour in women having a caesarean section which can alter the CTG interpretation. Furthermore, background maternal information was not accounted for, however it is already well known that a combination of risk factors such as nulliparity, prolonged labor and gestational age >41 may increase risk of HIE.[34-36] The recording of maternal heart rate instead of fetal heart rate was present in 2 cases and this may also have introduced an error on group allocation. Finally, due to the sensitivity of these cases and the potential medico-legal implications access to data may have been limited.

Conclusion

We provide preliminary evidence for the association between types of hypoxia using physiological CTG interpretation and patterns of injury noted on neonatal cerebral MRI: chronic hypoxia was associated with total brain injury, gradually evolving and/or subacute hypoxia with watershed pattern of brain injury and acute hypoxia was associated with BGT

injury. Infants with CTG trace suggestive of chronic hypoxia or other antenatal injuries were overrepresented in this cohort and were also more likely to have a poor neurodevelopmental outcome.

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