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An Update of Our Understanding of Fetal Heart Rate Patterns in Health and Disease

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Understanding Fetal Heart Rate Patterns That May Predict Antenatal and Intrapartum Neural Injury

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Electronic fetal heart rate (FHR) monitoring is widely used to assess fetal well-being throughout pregnancy and labor. Both antenatal and intrapartum FHR monitoring are associated with a high negative predictive value and a very poor positive predictive value. This in part reflects the physiological resilience of the healthy fetus and the remarkable effectiveness of fetal adaptations to even severe challenges. In this way, the majority of "abnormal" FHR patterns in fact reflect a fetus' appropriate adaptive responses to adverse in utero conditions. Understanding the physiology of these adaptations, how they are reflected in the FHR trace and in what conditions they can fail is therefore critical to appreciating both the potential uses and limitations of electronic FHR monitoring.

Introduction

Fetal heart rate (FHR) patterns remain a critical index of fetal wellbeing throughout gestation and during labor. Its major limitation is that as currently used FHR monitoring has a very good negative predictive value but an extremely poor positive predictive value for fetal compromise, and so promotes excessive intervention. Lear and colleague argue that part of the problem is that current models of FHR interpretation are complex and do not have a strong physiological basis.[1] They reviewed the determinants of injury, including maturity, the pattern of exposure to HI, impaired placental function, often associated with fetal growth restriction and in the long-term, socio-economic deprivation. The key conclusion from this systematic review of experimental studies by Lear and colleagues was that neural injury before and during labor is tightly linked to the onset and duration of fetal hypotension during hypoxia, across multiple species and paradigms.[1] The obvious question is whether subtle changes in FHR over time can be used to identify the onset of hypotension.

Intrapartum Fetal Heart Rate Patterns

The most common, potentially pathological change in the FHR in labor is the appearance of rapid falls ("decelerations") during uterine contractions. For many years, compression of the fetal head was hypothesized to mediate so called "early" decelerations, that is to say decelerations that with a fall in FHR that parallels each contraction and resolves as the contraction ends. A systematic review showed that when it occurs, fetal head compression is not necessarily benign but does not seem to be a common contributor to intrapartum decelerations.[2] Rather, there is compelling evidence that FHR decelerations are mediated by reduced utero-placental gas exchange leading to rapid falls in fetal oxygenation triggering the fetal peripheral chemoreflex.[3] Thus, a FHR deceleration just means that the fetus is showing a reflex response to a moderate to deep fall in oxygenation. Further, new evidence in fetal sheep now shows confirms that other postulated reflexes such as the Bezold-Jarisch reflex[4] and the baroreflex[5] are not able to trigger decelerations typical of those observed in human labor.

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The fetal chemoreflex becomes attenuated after about 60-90 seconds during acute, severe hypoxia; thereafter bradycardia is maintained by direct effects of myocardial hypoxia. In a controlled study of parasympathetic blockade with atropine in near-term fetal sheep, the peripheral chemoreflex was shown to completely control brief decelerations at a time when fetuses were maintaining normal to increased arterial pressure.[6] The peripheral chemoreflex initiated decelerations throughout the study, but after the onset of evolving fetal hypotension myocardial hypoxia increasingly sustained decelerations.

Encouragingly, in a systematic study of brief repeated occlusions of the umbilical cord in near-term fetal sheep, the cumulative area of decelerations and the related parameter, deceleration capacity predicted the development of hypotension at a median of 103 and 123 minutes before the final occlusion, respectively.[7] This observation supports the potential of computerized monitoring to improve identification of fetuses at risk of hypotension leading to hypoxic-ischemic injury during labor. However, it is important to note that fetal growth restriction is a common antecedent of perinatal brain injury.[8] In fetal sheep with chronic hypoxemia, deceleration area and capacity were much less effective in predicting fetal hypotension than in previously normoxic fetuses[9]; this is an important limitation, suggesting that even computerized monitoring will require adjustment.

Fetal Heart Rate Variability

Changes in fetal heart rate variability (FHRV) are widely used to evaluate fetal adaptation to labor. In the healthy, normoxic fetus, it reflects the interplay between sympathetic and parasympathetic. During brief, repeated labor-like hypoxemia though, sympathetic activity becomes completely suppressed, so that FHRV between occlusions is entirely mediated by the parasympathetic system.[10,11] Contrary to most current clinical protocols, FHRV tends to be increased between decelerations in studies in near-term fetal sheep. Consistent with this finding, there is now emerging clinical evidence that increased FHRV during labor may be an underappreciated warning sign of fetal compromise.[12] More research is clearly needed.

Perinatal Infection

Antenatal and intrapartum infection increase the risk of preterm birth and perinatal brain injury.[13] Diagnosis of even overt infection is still largely limited to soft clinical signs, while chorioamnionitis is most often asymptomatic. There is still little understanding of the independent effect of fetal inflammation on FHR patterns.

In preterm fetal sheep, progressive inflammation, with doubling of lipopolysaccharide infusions every 24 hours for 5 days was associated with modest increases in interleukin-6 and did not lead to fetal hypotension or altered FHRV measures,[14] but was associated with MRI and histological evidence of white matter injury.[15] In contrast, a model that includes repeated high-dose exposure to lipopolysaccharide (to model an acute fetal inflammatory response) triggered a significant release of interleukins 6, 10, and tumor necrosis factor, cardiovascular compromise and hypotension.[16] Fetuses that developed hypotension showed an evolving pattern of initial increased FHR variability (FHRV), followed by the late appearance of suppressed FHRV, as measured by time and frequency domain measures.

Collectively these findings suggest that fetuses at highest risk of cardiovascular dysfunction and mortality are the most likely to show abnormal FHR patterns, whereas slower, progressive infections may not alter FHR patterns. In turn, this finding is consistent with evidence that a significant number of neonates with culture-positive sepsis were not identified by heart rate monitoring,[17] highlighting the need for further biomarkers for subtle perinatal infections.

Antenatal Hypoxia-Ischemia

Hypoxia-ischaemia before birth is a key risk factor for stillbirth and severe neurodevelopmental disability in survivors, including cerebral palsy.[18,19] However, there is a lack of reliable biomarkers to detect at risk fetuses that may have suffered a transient period of severe HI. In a study of 3 weeks recovery after severe HI in preterm fetal sheep acute HI that is known to lead to evolving severe white and grey matter injury over 3 weeks,[20] time and frequency domain measures of FHRV were suppressed, with loss of circadian rhythms during the first 3 days after HI.[21] The circadian rhythms progressively recovered, but over the final 2 weeks of recovery after HI, there was a notable exaggeration of the circadian rhythms of frequency domain FHRV measures, as shown by lower morning nadirs but no change in the evening peak of FHRV. There is now evidence that this slowly evolving injury was attenuated by very delayed infusion of a tumor necrosis factor inhibitor 3 days after HI.[22] The obvious challenge is to identify infants who would benefit. Circadian changes in FHRV may be a low-cost, easily applied biomarker to identify infants who have been exposed to antenatal HI and evolving brain injury.

Conclusions

Assessment of FHR patterns is a critical index of fetal wellbeing, yet robust evidence for when FHR patterns transition from health to disease is still lacking. Although evidence derived from well-conducted clinical studies remains needed, animal studies provide an unparalleled access to the fetal physiological status underlying FHR patterns to help generate novel concepts to guide the design of future clinical studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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