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NARRATIVE REVIEW

Intrapartum foetal heart rate decelerations are physiological adaptations to hypoxia: a critical appraisal of the recent evidence.

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ABSTRACT

Electronic intrapartum foetal monitoring (also known as cardiotocography, CTG) is the standard technique to assess the foetal well-being during labour. In the last decade, several researchers have provided useful information regarding the pathophysiology of foetal heart rate (FHR) decelerations, the main CTG feature to cause interpretation disagreement; recent evidence summarized in this paper set new grounds to reconceptualize the “classical” aetiology of intrapartum foetal hypoxia and FHR decelerations. Each deceleration is generated from hypoxia, and it is the dynamic pattern of these decelerations that gives information about the status of metabolic and cardiac adaption mechanism of the foetus. The relationship to uterine contractions or the morphology of deceleration should no longer be used to discriminate a reassuring or non-reassuring CTG trace.

INTRODUCTION

Cardiotocograph (CTG) is a device that simultaneously records foetal heart rate (FHR) and uterine activity that was first introduced in 1968 [1] and is currently the most common antenatal and intrapartum method used to monitor foetal well-being. Evidence supporting its ability to predict and reduce neonatal morbidity and mortality is still scarce [2, 3], with a very low positive predictive value for both antenatal and intrapartum FHR monitoring. As a result, “normal” FHR patterns appear to be strongly associated with positive outcomes, while “abnormal” FHR patterns are weakly associated with negative outcomes [4].

The main CTG feature that misleads physicians and midwives is the FHR deceleration; many experts have studied the biological mechanisms underlying decelerations, thus leading to three different known “classical” patterns of FHR deceleration: early, late and variable [5].

Each of these patterns has been associated with a different etiological origin, outcome, and management options, as suggested by national and international guidelines [6-8].

In this scenario, CTG-based disagreement is a major source of obstetrical litigation due to the extensive use of intrapartum CTG monitoring and the difficulty and ambiguity of its interpretation [9].

The purpose of this review is to analyse the physiology of foetal intrapartum hypoxia and its CTG phenotype, namely FHR decelerations.

FOETAL PHYSIOLOGY

The foetus constantly lives its intrauterine life with a very low partial pressure of arterial O₂ (around 30 mmHg) and perfectly compensates this hypoxia using both basal and acute defence mechanisms. The basal mechanisms consist of higher basal flow to organs, different structure of foetal haemoglobin, a more sensitive Bohr effect and more vascular

shunts to facilitate redistribution of blood flow to central organs. In cases of abrupt falls in O_2 tension, the foetus also activates metabolic adaptations to reduce oxygen consuming pathways, coordinated by the peripheral chemoreflex, such as bradycardia, reducing body movements and switching to quiet sleep.

Given the similarity of O_2 and CO_2 tension in umbilical vein and uterine vein, it is reasonable to believe that gas exchange via the human placenta is a mechanism that is perfusion-limited rather than diffusion-limited. The mechanism behind gas exchange between maternal and foetal circulation is also suggested by the shape of placental terminal villi, as the branch-like shape of foetal vessels increases the area designated for gas exchange and allows a slower blood flow, maximizing the duration of the transport process [10].

Assuming that foetal blood oxygenation and decarboxylation are strongly dependent on placental blood perfusion, it has been postulated that foetal O_2 uptake is tightly related to placental O_2 delivery.

Uterine contractions periodically interrupt the intervillous circulation, which in turn decreases blood flow, reduces O_2 delivery to the placenta, and generates hypoxaemia and foetal hypoxia as described in recent studies using either Doppler and magnetic resonance imaging (MRI) techniques [11-13]; uterine hyperstimulation, defined as increased number [14] and intensity of contractions and increased resting tone between them, is a critical CTG feature to beware of when interpreting a CTG trace, as it is generally associated with deterioration of FHR patterns, higher rates of NICU admission and composite neonatal outcomes [15, 16].

The correct functioning of the exchange mechanism is guaranteed by the refreshment of placental circulation, which is cyclically impaired by uterine activity, making uterine contractions the initiating event behind most of sub-acute hypoxic foetal damage. Despite that, after abrupt changes in uterine oxygen supply brought by a partial occlusion of the

terminal branches of the uterine artery, placental oxygen consumption remains remarkably constant thus hampering the oxygen fraction that is to be delivered to the foetus [17].

The evaluation of a CTG trace is therefore necessarily indissociable from a correct uterine tone registration and interpretation, as each contraction, even subclinical (Braxton Higgs), is a potential stressor that could lead to foetal hypoxemia, as shown in MRI studies [11, 12].

FOETAL HEART RATE DECELERATIONS

Decelerations have been historically classified in “early”, “late”, and “variable”, according to their temporal relationship with uterine contractions [5-8]; early decelerations (“repetitive and periodic slowing of the foetal heart rate with onset early in the contraction and return to baseline at the end of the contraction”) were thought to result from head compression; variable decelerations (“intermittent and periodic slowing of the foetal heart rate with a variable time in relation to the contraction”) were supposed to be produced by umbilical cord compression; late decelerations (“repetitive and periodic slowing of the foetal heart rate with onset mid to end of the contraction and the lowest point more than 20 seconds after the peak of the contraction, and ending after the contraction”) were the only type of decelerations linked to foetal hypoxia.

This classical etiological classification has been recently questioned by physiologists, who set new foundations for the re-conceptualization of decelerations [18].

The reflexes historically hypothesized to be triggered during labour are the head baroreflex for early decelerations, the Bezold-Jarisch reflex and the peripheral baroreflex for variable decelerations and chemoreflex for late decelerations.

Early decelerations have been hypothesized to be triggered by intracranial baroreflex activation due to foetal head compression during labour [19, 20]; accordingly, most guidelines consider these decelerations to be benign and unrelated to hypoxia. There is no

evidence to support any theories that the foetal reaction to head compression is caused by the stretching of the dural ligaments or other non-hypoxic processes.

According to an expert review, the impact of foetal head compression on the foetus metabolism is controversial, and it is only rarely associated with deceleration. The authors suggest that the foetus has the ability to adapt to increased intracranial pressure maintaining appropriate cerebral perfusion during labour, through the activation of the intracranial baroreflex, except in the setting of prolonged systemic hypoxemia [21]. Therefore, the peripheral chemoreflex and intracranial baro(chemo)reflex work synergistically during labour to maintain cerebral oxygen supply; the Cushing response is the “terminal” part of a much larger “intracranial reflex” that only activates when there is significant cerebral hypoperfusion. Recently published research showed that astrocytes detect falling oxygen tension and cerebral perfusion pressure and activate central nervous system (CNS) autonomic sympathetic control circuits to increase systemic arterial blood pressure and heart rate with the purpose of maintaining brain blood flow and oxygen delivery [22]. Therefore, when foetal head compression leads to a deceleration, this phenomenon is consistent with a Cushing response, a near terminal response to reduced cerebral blood flow secondary to increased intracranial pressure, reflecting severe cerebral hypoperfusion and should not be considered as reassuring. According to current evidence, what used to be defined as early deceleration can no longer be linked to the previously acknowledged physiological mechanism (*i.e.*, Cushing Reflex) but has to be correlated with some form of foetal response to hypoxia.

Variable decelerations are thought to be triggered by umbilical cord compression, with compression of the umbilical vein (Bezold-Jarisch reflex, consisting of bradycardia following reduction of preload in order to increase cardiac filling time) and umbilical arteries (afterload increase and baroreflex-mediated inhibitory response with foetal heart rate deceleration).

Bezold-Jarisch reflex has been hypothesized to be a possible cause of variable decelerations, but evidence from different studies showed that this reflex did not appear to be activated by reduced preload and when activated it was responsible for decelerations with different morphology [23, 24]. Moreover, Bezold-Jarisch reflex has been demonstrated to have a markedly delayed postnatal maturation. A recent case-control study evaluated the effects of repeated umbilical cord compressions in foetal sheep who either underwent or not bilateral cervical vagotomy and demonstrated that the idea that labour-like umbilical cord occlusion (UCO) could hinder ventricular filling is incompatible with higher carotid and femoral blood flows following vagotomy, which are consistent with increased left and right ventricular output. Overall, the study provides evidence supporting the hypothesis that Bezold-Jarisch reflex is not activated by UCO [25].

Recent studies have illustrated that deep, rapid decelerations such as variable ones cannot be explained by activation of the baroreflex alone. According to Lear and colleagues [26], who compared the morphology of FHR decelerations in near-term foetal sheep after administration of phenylephrine or brief-UCOs, the peripheral chemoreflex is the main mediator of FHR decelerations and the baroreflex only has a limited role in the first 3-4 sec of the UCO. Furthermore, the baroreflex response is sympatho-inhibitory and leads to peripheral vasodilatation, and therefore it cannot explain the intense peripheral vasoconstriction registered during acute umbilical cord occlusion. These results provide strong evidence in favour of the hypothesis that rapid FHR decelerations in labour are primarily mediated by peripheral chemoreflex activation in response to abrupt falls in foetal oxygenation.

THE PERIPHERAL CHEMOREFLEX

The peripheral chemoreflex is the response to an acute fall in oxygen tension mediated by the peripheral chemoreceptors. These receptors detect hypoxia and activate a rapid

parasympathetic-mediated fall in heart rate and a sympathetic-mediated peripheral vasoconstriction. The combined effect of these responses maintains or increases arterial pressure, which consequently maintains or increases blood flow to the noble organs such as the brain, heart and adrenals [27].

In the extra-uterine life, when oxygen availability can be increased by hyperventilation, vasodilatation and increased heart rate occur to support systemic perfusion. On the other hand, in foetal life when oxygen availability is limited to the placental storage, the primary chemoreflex response of bradycardia and peripheral vasoconstriction prevails to decrease cardiac oxygen consumption and/or redistribute the available oxygen supply.

Therefore, it is likely that the decrease in FHR during intrapartum foetal hypoxia or foetal asphyxia are instances of this complex cardiovascular physiological strategic response to oxygen shortage. These foetal compensatory responses are physiological and not pathophysiological, and it is a necessary skill for a physician to be able to recognize when, after repeated hypoxic insults, the pattern of deceleration evolves into cardiovascular decompensation [28].

FOETAL CARDIOVASCULAR DECOMPENSATION

The research by Lear and colleagues [29] provided evidence supporting the idea that hypoxia generated by repeated umbilical cord occlusions (labour-like uterine activity) is generally well tolerated in healthy individuals, such as fetuses with adequate placental circulation and oxygen supply, because the inter-contraction hematic intervillous refreshment enables a correct disposal of the hypoxic debt.

Hypoxia is detected by the peripheral chemoreceptors that trigger foetal heart rate deceleration and peripheral vasoconstriction to reduce cardiac workload, increase cardiac filling time, diastolic coronary perfusion time, and promote oxygenated blood redistribution to noble organs.

Chronic conditions like gestational diabetes mellitus, foetal growth restriction or preeclampsia can alter the regular villous tree geometry [30], reduce placental oxygen supply, and jeopardize the physiological mechanisms of foetal response to intrapartum hypoxia. The severity of hypoxia and the ability of the foeto-placental unit to answer the foetal metabolic demands are key factors in the foetal cardiovascular compensation.

The failure of the foetal autonomic responses to recurrent severe hypoxia does not appear to be the cause of foetal metabolic acidosis and hypotension after hypoxic insults that occur repeatedly. In fact, the development of severe foetal compromise is associated with augmentation of this response, as shown by the progression of tachycardia and an increase in the slope and absolute magnitude of the FHR decline [31].

The shift from physiology to pathophysiology reveals itself when the inter-contraction disposal of metabolites does not allow a sufficient recovery from hypoxia. Once decompensation takes over, decelerations become steeper and deeper and are associated with changes in the baseline: these are signs that hypotension is establishing. If the oxygen supply is sufficient for the foetus to compensate, the chemoreflex-mediated response to hypoxia is characterized by a reduction of foetal heart rate associated with hypertension; when the oxygen availability runs out, the repeated chemoreflex-mediated decelerations progressively deplete glycogen myocardial storage, generating myocardial stunning and gradual failure, leading to hypotension. Progressive foetal decompensation during labour is not related to the failure of autonomic adaptation, but to a combination of exhaustion of myocardial glycogen and evolving cardiac stunning [29, 32].

NEW INSIGHTS INTO INTERPRETATION OF FHR DECELERATIONS

According to this hypothesis, during the interpretation of an intra-partum cardiotocographic tracing it is important to consider the depth, frequency, and duration of decelerations, not the shape and interaction with uterine contractions; it is still unknown when exactly the

aetiology of foetal heart rate decelerations switches from the peripheral chemoreflex to myocardial failure [33].

On the other hand, recent insights into foetal physiology are providing us new tools to better evaluate the foetal basic-acid equilibrium. The parameters of depth, frequency and duration of decelerations are included in the assessment of deceleration area and deceleration capacity, which have been demonstrated to strongly correlate with acidaemia [34]; in the research from Cahill and colleagues, deceleration area was the most predictive parameter of acidaemia, and in combination with any 10-minute period of heart rate baseline tachycardia, it was predictive of neonatal morbidity, even when periods of moderate variability were present [34]. Deceleration area was calculated as an integral mathematic function that can be simplified to the sum of the areas of deceleration (each deceleration being calculated as depth times duration divided by two) in the last 120 minutes of the CTG trace.

The ability of deceleration area and capacity to better identify foetuses at risk of hypotension that might result in hypoxic-ischaemic damage during childbirth is also supported by a recent, prospective work by Georgieva and colleagues [35] who demonstrated that these two parameters are strongly associated with developing foetal hypotension, significantly increasing in the group of foetal sheep who received more frequent UCOs.

CONCLUSIONS

Very weak evidence supports the common beliefs behind the different aetiology of deceleration. Accordingly, FHR decelerations should no longer be categorized as “pathological” or “benign”, as foetal hypoxia appears to represent the physiological adaptation of the foetus to uterine contractions and the source of the majority of decelerations.

The healthy foetus can easily adapt to mild reduction of oxygen supply without triggering a deceleration, but not every foetus approaches labour with a sufficient placental oxygen reservoir. Given the same intensity of uterine activity, different foetuses will display different FHR tracings.

Disregarding this assumption, most guidelines provide similar patterns (and management options) of FHR decelerations [36] to apply indiscriminately to every foetus, despite their pre-labour metabolic condition, and not considering the dynamic features of evolving hypoxia and subsequent changes in the CTG trace.

In this scenario, a recent meta-analysis involving almost 50000 foetuses [37] has highlighted that 98% of “traditional” category II CTG tracings are not associated with adverse foetal outcomes; this finding addresses a very concerning issue about the practical use of intrapartum foetal monitoring, unravelling the fact that conventional CTG interpretation probably needs to be reconceptualized, based on the recently available physiological and pathophysiological evidence [38].

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

R.B., A.S., F.Z., D.DiM.: Conceptualization. R.B., A.S., F.Z., S.S., D.DiM.: Investigation. E.D'A., V.D.: Methodology. R.B., L.M.: Project administration. A.G.: Resources. R.B., F.P., P.G., A.G.: Supervision. R.B., V.D'A.: Validation. A.S., F.Z., S.S.: Writing – original draft. R.B., D.DiM.: Writing – review & editing.

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The authors declare that they have no conflict of interests.

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