Journal of Perinatology (2020) 40:56–62
https://doi.org/10.1038/s41372-019-0520-9

ARTICLE

Marked variability in intrapartum electronic fetal heart rate patterns: association with neonatal morbidity and abnormal arterial cord gas

Brock Polnaszek[1] · Julia D. López[1] · Reece Clark[1] · Nandini Raghuraman[1] · George A. Macones[2] · Alison G. Cahill[2]

Received: 12 August 2019 / Revised: 12 September 2019 / Accepted: 23 September 2019 / Published online: 2 October 2019

Abstract

Objective Investigate marked variability in fetal heart rate (FHR) patterns before delivery and its association with neonatal morbidity and abnormal arterial cord gases.

Study design Prospective cohort of laboring patients at term. Composite neonatal morbidity (respiratory distress, mechanical ventilation, suspected sepsis, meconium aspiration syndrome, therapeutic hypothermia, hypoxic-ischemic encephalopathy, seizure, and death) and abnormal arterial cord gases (pH < 7.10, lactate ≥ 4 mmol/L, base deficit < −12 mEq/L) were assessed with multivariable logistic regression.

Result Three hundred and ninety (4.5%) neonates had marked variability in FHR patterns before delivery. There was no difference in composite neonatal morbidity (aRR 1.22; 95% CI 0.91–1.63), though neonates with marked variability in FHR patterns were more likely to have a respiratory distress (aRR 1.85; 95% CI 1.25–2.70). There was an increased risk of composite abnormal arterial cord gases (aRR 1.66; 95% CI 1.47–1.88).

Conclusion Marked variability in FHR patterns was not associated with composite neonatal morbidity but was associated with abnormal arterial cord gases.

Introduction

Electronic fetal heart rate (FHR) patterns are ubiquitously used to monitor fetal well-being in the United States during labor [1, 2]. The three-tiered *Eunice Kennedy Shriver* National Institute of Child Health and Human and Development (NICHD) system for categorizing FHR patterns is used to identify those neonates at risk of developing neonatal acidemia and subsequent morbidity [3] (Table 1). One ongoing challenge in obstetrics is balancing the indeterminate fetal risk with category II monitoring versus maternal risk of operative delivery [1, 2, 4]. Furthermore, >80% of fetuses will experience a category II tracing during labor [2].

Within the FHR tier system, category II remains the largest category of FHR with the greatest degree of uncertainty as it pertains to intrapartum well-being. One specific example of a category II features with very limited research is marked variability in FHR patterns [5–10]. FHR variability is thought to be a reflection of the sympathetic and parasympathetic nervous system [3]. The existing literature demonstrates that moderate variability reliably in FHR patterns predicts the absence of damaging degrees of hypoxia-induced metabolic acidemia at the time it is observed [11]. The significance of marked variability in FHR patterns; however, maybe a normal variant or an exaggerated autonomic response to transient interruption of fetal oxygenation. For example, marked variability in FHR patterns have been observed with seizures in human and sheep studies after a terminal hypoxic event [12]. Clarifying the significance of marked variability in FHR patterns may aid clinicians when balancing the fetal risk of acidosis/morbidity versus maternal risk of operative delivery, particularly during a category II FHR pattern.

Given the widespread use of FHR but a limited literature on the significance of marked variability in FHR patterns,

Presented at the 39th Annual Scientific Meeting of the Society for Maternal Fetal Medicine, February 15th, 2019 in Las Vegas, Nevada.

✉ Brock Polnaszek
brock.polnaszek@wustl.edu

[1] Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, Washington University in Saint Louis School of Medicine, Saint Louis, MO, USA

[2] The University of Texas at Austin Dell Medical School, Austin, TX, USA

Table 1 Three-tier fetal heart rate interpretation system[a]

Category I
Category I fetal heart rate (FHR) tracings include all of the following
Baseline rate: 110–160 beats per minute
Baseline FHR variability: moderate
Late or variable deceleration: absent
Early decelerations: present or absent
Accelerations: present or absent
Category II
Category II FHR tracings include all FHR tracings not categorized as Category I or Category III. Category II tracings may represent an appreciable fraction of those encountered in clinical care. Examples of Category II FHR tracings include any of the following:
Baseline rate
Bradycardia not accompanied by absent baseline variability
Tachycardia
Baseline FHR variability
Minimal baseline variability
Absent baseline variability not accompanied by recurrent decelerations
Marked baseline variability[b]
Accelerations
Absence of induced accelerations after fetal stimulation
Periodic or episodic decelerations
Recurrent variable decelerations accompanied by minimal or moderate baseline variability
Prolonged deceleration more than 2 min but less than 10 min
Recurrent late decelerations with moderate baseline variability
Variable decelerations with other characteristics, such as slow return to baseline, "overshoots," or "shoulders"
Category III
Category III FHR tracings include either
Absent baseline FHR variability and any of the following
Recurrent late decelerations
Recurrent variable decelerations
Bradycardia
Sinusoidal pattern

[a]Modified from Macones et al. [3]

[b]Defined as neonates with marked variability in FHR patterns at any time point in the 120 min before delivery

our objective was to investigate the incidence before delivery and to examine the risk of neonatal morbidity and abnormal arterial cord gases.

Materials and methods

This is a planned secondary analysis of a single-center, prospective cohort study of all consecutive women in labor at term with a singleton, nonanomalous infant from 2010 through 2015 [7]. The objective of the primary study was to describe the frequency of FHR patterns seen in labor using modern nomenclature and to test the hypothesis that visually interpreted patterns are associated with acidemia and morbidity in term infants. The Washington University School of Medicine Human Research Protection Office approved this study prior to enrolment (IRB number 201102438). Universal continuous FHR patterns and arterial umbilical cord gases including lactate at delivery are collected as a standard of care at our institution. Patients were included in this study if they had sufficient FHR patterns, defined as at least 30 min of FHR patterns in the 120 min prior to delivery. This definition enabled generalizability and prevented exclusion of cases where clinical events (e.g., epidural placement, precipitous labor) precluded optimization of continuous monitoring. Excluded were women who were not in labor, not at term gestation, had a multi-fetal gestation, did not have continuous FHR recording, and neonates from whom umbilical artery (UA) blood samples were not obtained.

The primary outcomes were a composite (1) neonatal morbidity and (2) abnormal arterial cord gases. Composite neonatal morbidity consisted of ≥1 of the following: Respiratory distress, mechanical ventilation, suspected sepsis, meconium aspiration syndrome, therapeutic hypothermia, hypoxic-ischemic encephalopathy, seizure, and death. Respiratory distress was defined as nasal flaring, subcostal, and intercostal retractions, and need for supplemental oxygen to maintain oxygen saturation >95% without a specified duration of time. Composite abnormal arterial cord gases was defined as ≥1 of the following: UA pH < 7.10, UA lactate ≥4 mmol/L, UA base deficit < −12 mEq/L. UA lactate is universally collected at our institution secondary to the association with neonatal morbidity [13, 14] as well as venous blood gases to ensure validity. UA artery and vein samples were collected by trained and experienced providers. Using historical data from our institution, the accuracy of this collection is >90% [13, 15]. An UA pH of <7.10 was selected as an attempt to identify term fetuses who have developed abnormal pH. Information regarding maternal characteristics, antenatal care, labor outcomes, and neonatal diagnoses were collected from medical records by trained research staff.

FHR patterns in the final 120 min prior to delivery were interpreted in 10-min epochs by trained obstetric research nurses with a high inter-observer and intra-observer reliability [7]. Epochs of 10-min were selected based on the NICHD definitions of fetal heart parameters. The obstetric research nurses performed blinded assessments of 30 FHR tracings after every 500 patients during the course of the study, with a range of kappa of 0.83–0.95. [7] FHR recordings were obtained with external and internal monitors, as clinically indicated. Five elements of the FHR were extracted using strict and unambiguous definitions from the NICHD criteria. Marked variability in FHR patterns was defined as fluctuations in FHR amplitude of >25 beats per minute based on 10-min epochs, excluding accelerations and decelerations from baseline. Baseline clinical characteristics between neonates with and without marked variability in FHR patterns were compared using χ^2 test or

Fisher exact test for categorical variables and Mann–Whitney *U* test or Student's *t* test for continuous variables, as appropriate. Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for each of the outcomes of interests. Multivariable logistic regression was used to adjust for pertinent confounding variables, which were identified by those variables that had at least a 10% effect size on the RR or were clinically relevant as confounders. All analyses were performed using SAS 9.4 for Windows.

Results

Of the 14,450 enrolled in the primary study, 5,870 were excluded (2,861 preterm births, 1,505 cesarean prior to labor, 530 had insufficient FHR, 298 major anomalies, 294 multiple gestation, 373 lacked UA pH, and 9 were incarcerated) leaving a final cohort of 8,580. Among the final cohort of 8,580, 390 (4.5%) or ~1 in 20 neonates had marked variability in FHR patterns at any time point in the 120 min prior to delivery while 8,190 (95.5%) did not (Fig. 1). Acidemia defined as UA pH <7.10 was rare and occurred in 149 (1.7%) of the neonates. Of those neonates with acidemia, 10/149 (6.7%) of neonates had marked variability in FHR patterns before delivery while 139/149 (93.3%) did not (Fig. 1). Neonates who had marked variability in FHR patterns were born to women who were younger, more likely to be nulliparous and obese, compared with neonates without marked variability in FHR patterns (Table 2). Neonates with marked variability in FHR patterns were also more likely to be born to women who had their labor induced and deliver via an operative or cesarean section. Neonates with marked variability in FHR patterns were more likely to have a lower UA pH, higher UA pCO2, higher UA bicarbonate, and more UA base deficit compared with those neonates born without marked variability in FHR patterns. There were no differences in neonatal Apgar

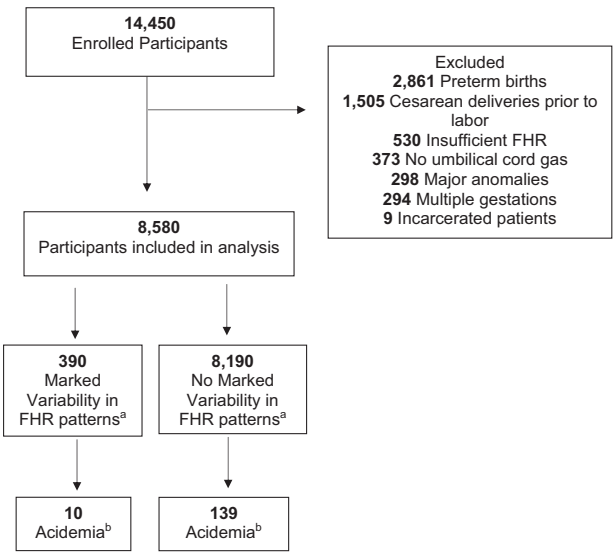

Fig. 1 Flowchart of study participants. **a** Marked variability in FHR patterns was defined as fluctuations in FHR amplitude of >25 beats per minute based on 10-min epochs, excluding accelerations and decelerations from baseline in the last 120 min. **b** Acidemia defined as umbilical artery pH < 7.10

Table 2 Baseline characteristics among women and neonates with and without marked variability in FHR patterns in the last 120 min before delivery ($n = 8{,}580$)[a]

Characteristic	Marked variability in FHR patterns[b] ($n = 390$)	No marked variability in FHR patterns ($n = 8{,}190$)	*P*-value[c]
Maternal age, years	25.0 ± 6.0	25.8 ± 5.9	0.01
Maternal age ≥ 35, years	29 (7.4)	735 (9.0)	0.30
Gestational age at delivery, weeks	39.2 ± 1.3	38.9 ± 1.2	<0.01
Nulliparous	215 (55.1)	3,456 (42.2)	<0.01
Race			0.26
African American	267 (68.5)	5,298 (64.7)	
Caucasian	79 (20.3)	1,862 (22.7)	
Latina	23 (5.9)	590 (7.2)	
Body mass index (kg/m^2)	33.5 ± 7.9	32.2 ± 7.3	<0.01
Labor			<0.01
Spontaneous	190 (48.7)	4,603 (56.2)	
Induction	200 (51.3)	3,587 (43.8)	
Any hypertensive disorder	68 (17.4)	1,394 (17.0)	0.83
Gestational diabetes	6 (1.5)	255 (3.1)	0.08
Pregestational diabetes mellitus	4 (1.0)	119 (1.5)	0.49
Oligohydramnios	10 (2.6)	122 (1.5)	0.23
Prior cesarean	36 (9.2)	725 (8.9)	0.80
Prostaglandin use	79 (20.3)	1,449 (17.7)	0.20
Foley bulb use	51 (13.1)	928 (11.3)	0.29
Oxytocin use	14 (3.6)	351 (4.3)	0.03
Birthweight, grams	3,281 ± 441	3,241 ± 464	0.09
Mode of delivery			
Vaginal	247 (63.3)	6,458 (78.9)	<0.01
Operative vaginal	42 (10.8)	370 (4.5)	<0.01
Cesarean	101 (25.9)	1,362 (16.3)	<0.01
Umbilical arterial cord gases			
pH	7.2 ± 0.07	7.3 ± 0.06	<0.01
pCO2	57.1 ± 9.8	54.6 ± 9.8	<0.01
HCO3	3.9 ± 1.6	3.3 ± 1.6	<0.01
Base deficit	−3.9 ± 2.6	−3.0 ± 2.6	<0.01
Apgar < 7 at 5 min	13 (3.3)	195 (2.4)	0.23

Data are number (percent) or mean ± standard deviation

[a]Excludes preterm births, cesarean prior to labor, insufficient FHR, major anomalies, multiple gestation, no UA pH, and incarcerated women

[b]Defined as neonates with marked variability in FHR patterns at any time point in the 120 min before delivery

[c]*P* values based on Student *t* test, Fisher's exact test, and χ^2

Table 3 Association between neonatal morbidity and abnormal arterial cord gases among neonates with and without marked variability in FHR patterns in the last 120 min before delivery ($n = 8,580$)[a]

	Marked[b] variability in FHR patterns ($n = 390$)	No marked variability in FHR patterns ($n = 8,190$)	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio[c] (95% CI)
Composite neonatal morbidity[d]	43 (11.0)	714 (8.7)	1.26 (0.95, 1.69)	1.22 (0.91, 1.63)
Respiratory distress	28 (7.2)	304 (3.7)	1.93 (1.33, 2.81)	1.85 (1.26, 2.70)
Mechanical ventilation	3 (0.8)	47 (0.6)	1.34 (0.42, 4.29)	1.34 (0.42, 4.30)
Meconium aspiration syndrome	3 (0.8)	19 (0.2)	3.32 (0.98, 11.16)	3.14 (0.93, 10.56)
Suspected sepsis	34 (8.7)	593 (7.2)	1.20 (0.87, 1.68)	1.15 (0.82, 1.61)
Hypoxic-ischemic encephalopathy	0 (0.0)	35 (0.4)	–	–
Therapeutic hypothermia	1 (0.3)	41 (0.5)	0.51 (0.07, 3.71)	0.48 (0.07, 3.50)
Seizures	0 (0.0)	18 (0.2)	–	–
Neonatal death	0 (0.0)	4 (0.1)	–	–
Composite abnormal arterial cord gas[e]	162 (41.5)	2,050 (25.0)	1.66 (1.47, 1.88)	1.66 (1.47, 1.88)
Base deficit (<−12)	3 (0.8)	54 (0.7)	1.16 (0.36, 3.73)	1.16 (0.36, 3.69)
Acidemia (pH < 7.10)	10 (2.6)	139 (1.7)	1.51 (0.80, 2.85)	1.50 (0.80, 2.84)
Elevated lactate (≥4)	162 (41.5)	2,043 (25.0)	1.65 (1.46, 1.87)	1.66 (1.47, 1.88)

Data are number (percent)

[a]Excludes preterm births, cesarean prior to labor, insufficient FHR, major anomalies, multiple gestation, no UA pH, and incarcerated women

[b]Defined as neonates with marked variability in FHR patterns at any time point in the 120 min before delivery

[c]Adjusted for advanced maternal age and obesity

[d]Includes death, therapeutic hypothermia, mechanical ventilation, respiratory distress, meconium aspiration syndrome, seizures, suspected sepsis, and hypoxic-ischemic encephalopathy

[e]Includes base deficit < −12, umbilical artery acidemia pH < 7.10, or elevated lactate ≥4 mmol/L

scores regardless of the presence or absence of marked variability in FHR patterns (Table 2).

Of the 8,580 neonates in our cohort, 757 (8.8%) had the composite neonatal morbidity, while 2,212 (25.8%) had the composite abnormal arterial cord gases. After adjusting for advanced maternal age and obesity, neonates with marked variability in FHR patterns in the 120 min prior to delivery did not have increased risk of the composite neonatal morbidity (11% vs 8.7%, adjusted risk ratio (aRR) 1.22, 0.91–1.63) but they did have increased risk of composite abnormal arterial cord gases (41.5% vs 25%, aRR 1.66, 1.47–1.88) (Table 3). Among the individual components of the composites, neonates with marked variability in FHR patterns had increased risk for respiratory distress (7.2% vs 3.7%, aRR 1.85, 95% CI 1.26–2.70). The increased risk of composite abnormal arterial cord gases was largely driven by elevated lactate (41.5% vs 25.0%, aRR 1.66, 1.47–1.88). In addition, after adjusting for operative delivery, maternal age, and obesity, neonates with marked variability in FHR patterns continued to have increased risk of respiratory distress (aRR 1.56, 1.07–2.27) and elevated UA lactate (aRR 1.61, 1.43–1.83). There was no difference in the other individual components of the composite outcomes (Table 3).

Marked variability in FHR patterns occurred more frequently as delivery became closer over the 120 min (Fig. 2).

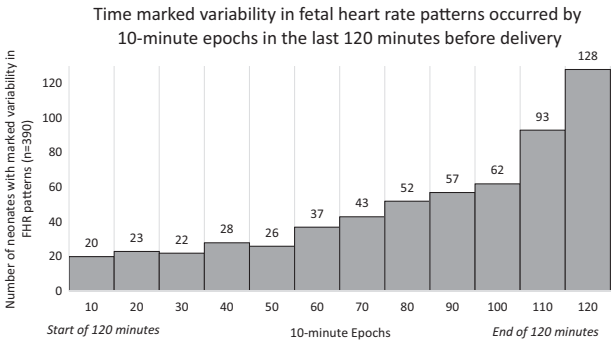

Fig. 2 Time marked variability in FHR patterns occurred by 10-min epochs in the last 120 min before delivery ($n = 390$)

There was no significant relationship with when marked variability in FHR patterns occurred and neonatal acidemia during the 120 min prior to delivery. This remained true for any individual 10-min epoch or when grouped in 30 min increments prior to delivery (Table 4). Furthermore, in an exploratory analysis, regardless of internal or external fetal monitoring (i.e., fetal scalp electrode 19 vs 130 of 149 neonates with acidemia, respectively) there was no association with between marked variability in FHR patterns and acidemia over time.

Table 4 Relationship between time marked variability in FHR patterns occurred and neonatal acidemia in the last 120 min before delivery ($n = 8{,}850$)[a]

Time of marked variability in FHR patterns prior to delivery, minutes[b] ($n = 390$)	Acidemia ($n = 10$)	No acidemia ($n = 380$)	P-value[c]
91–120	1 (0.7)	50 (0.6)	0.59
61–90	2 (1.3)	73 (0.9)	0.38
31–60	2 (1.3)	113 (1.3)	0.99
≤30	7 (4.7)	211 (2.5)	0.11

Data are in number (percent) and grouped epochs are not mutually exclusive

[a]Excludes preterm births, cesarean prior to labor, insufficient FHR, major anomalies, multiple gestation, lacked umbilical artery pH, and incarcerated women

[b]Defined as neonates with marked variability in FHR patterns at any time point in the 120 min before delivery

[c]Fisher exact tests

Discussion

Marked variability in FHR patterns is a rare component of FHR patterns occurring in 1 in 20 neonates during the 120 min prior to delivery in term neonates. Marked variability in FHR patterns was not associated with a composite neonatal morbidity. However, neonates with marked variability in FHR patterns in the 120 min prior to delivery had increased risk of respiratory distress and composite abnormal arterial cord gases that was largely driven by elevated UA lactate. Furthermore, there was no association over time between when marked variability in FHR patterns occurred in the 120 min prior to delivery and acidemia.

Our study builds on the limited literature on marked variability in FHR patterns. Triebwasser et al. demonstrated that neonates who underwent an operative delivery for nonreassuring fetal status had higher rates of marked variability in FHR patterns prior to initiation of the operative delivery compared with neonates undergoing operative delivery for other indications [8]. Siira et al. found that fetal heart variability as a continuous variable initially increased, but then decreased, in acidotic fetuses compared with controls in the last hour of monitoring before delivery. They suggested that the presence or absence of marked variability in FHR patterns, rather than timing of occurrence before delivery, is important for fetuses with acidemia [5]. Similar to our results, Liu et al. found an association between marked variability in FHR patterns and term neonatal respiratory morbidity (aOR 2.7; 95% CI 1.5–5.0) [6]. Our findings are congruent and build upon this previous research of marked variability in FHR patterns.

The association between marked variability in FHR patterns, neonatal anaerobic metabolism, and neonatal respiratory morbidity is biologically plausible. Marked variability in FHR patterns may represent an increased sympathetic response in the neonate due to a stressful intrapartum event (e.g., cord compression, meconium) that has not occurred with enough frequency or intensity to cause overt acidemia. Rather, it results in increased activity of the anaerobic pathway where lactate is synthesized as a byproduct. The rate of lactate synthesis is dependent on the activity of the anaerobic pathway and may be increased due to enhanced epinephrine activity (e.g., higher sympathetic nervous system response) or systemic illness [16]. In addition, elevated lactate used in our composite outcome is a strong predictor for neonatal morbidity at term [13, 14]. In vitro [17] and in vivo [18–23] studies have demonstrated an association between compromised lung tissue and elevated lactate both in animal and human studies. A net lactate production has been shown to lead to vasoconstriction of the pulmonary arterioles in humans, which at the time of delivery may impair oxygen exchange at the level of the alveoli resulting in respiratory distress in the neonate [24, 25]. It is plausible that this pathway may be at work in term infants with marked variability in FHR patterns in the 120 min prior to delivery even after controlling for known risk factors of elevated lactate (e.g., maternal obesity and operative delivery).

Limited research exists to guide clinicians and intrapartum management in the presence of marked variability in FHR patterns. Increasingly, research supports that not all category II tracings should be managed the same and that there is a wide spectrum of category II tracings that require careful interpretation [7, 26–28]. For example, the primary study by Cahill et al. found that total deceleration area is the most predictive FHR feature for acidemia and when combined with fetal tachycardia, significant neonatal morbidity. Furthermore, once the deceleration area threshold is reached, the number of cesareans needed to be performed to potentially prevent one case of acidemia and neonatal morbidity is five and six, respectively. Our findings do not support that marked variability in FHR patterns as an isolated characteristic is predictive of neonatal acidemia or composite neonatal morbidity. For example, many existing algorithms to help clinicians weigh risks and benefits for expedited delivery in category II tracings such as the one outlined by Clark et al. do not take marked variability in FHR patterns into account [26]. Meanwhile, another

management algorithm by Downs et al. suggests that you may observe or consider conservative measures (e.g., maternal position, discontinue oxytocin, administer oxygen, amnioinfusion, evaluate for infection, etc.) when marked variability in FHR patterns is encountered [28].

While intrapartum management of marked variability in FHR patterns was not clarified through this study, our study highlights the need for continued research of marked variability in FHR patterns in conjunction with other FHR patterns, particularly given the potential risk of respiratory issues following delivery. This information may be useful in hospitals with limited resources that may not have pediatricians or ancillary staff readily available for immediate respiratory support of the neonate at the time of delivery. Additional research is needed to validate and examine other FHR patterns such as relationship to uterine contractions, maternal pushing, and decelerations in combination with marked variability in FHR patterns as it relates to neonatal acidemia and neonatal morbidity.

The study's greatest strength is that it highlights and focuses on marked variability in FHR patterns as an under investigated and poorly described FHR characteristic within category II tracings. However, our study also has several limitations. First, our study examines the association between a rare FHR event and even more rare neonatal outcomes. This may underestimate the true risks of marked variability in FHR patterns on neonatal morbidity and acidemia as acidemia occurred in only 139 (1.6%) of neonates in our cohort. Second, our study is a secondary analysis from a single center which may represent biased internal interpretation and management of the FHR recordings that may not be universally applied. Third, there may be other maternal or intrapartum confounders not measured in our study cohort (e.g., drugs, other FHR patterns such as decelerations, relationship to contractions, maternal effort, fetal position in maternal pelvis) that may confound the associations we described. While our study builds on and supports a potential pathway between marked variability in FHR patterns, elevated lactate, and respiratory distress in term neonates, no practice changes should be implemented based on our findings and its limitations at this time.

Conclusion

In conclusion, marked variability in FHR patterns occurred in ~1 in 20 neonates before delivery and was not associated with increased risk of composite neonatal morbidity. However, marked variability in FHR patterns was associated with an increased risk of respiratory distress and elevated UA cord blood lactate.

Funding This work was funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) (R01HD061619-01, PI Cahill). Dr Cahill was a Robert Wood Johnson Foundation Faculty Physician Scholar, which partially supported this work. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official view of the NIH or Robert Wood Johnson Foundation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Gynecologists American College of Obstetrics and Gynecology. Practice bulletin no. 116: management of intrapartum fetal heart rate tracings. Obstet Gynecol. 2010;116:1232–40.
2. Jackson M, Holmgren CM, Esplin MS, Henry E, Varner MW. Frequency of fetal heart rate categories and short-term neonatal outcome. Obstet Gynecol. 2011;118:803–8.
3. Macones GA, Hankins GD, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines. Obstet Gynecol. 2008;112:661–6.
4. Hankins GD, Speer M. Defining the pathogenesis and pathophysiology of neonatal encephalopathy and cerebral palsy. Obstet Gynecol. 2003;102:628–36.
5. Siira SM, Ojala TH, Vahlberg TJ, Jalonen JO, Valimaki IA, Rosen KG, et al. Marked fetal acidosis and specific changes in power spectrum analysis of fetal heart rate variability recorded during the last hour of labour. BJOG. 2005;112:418–23.
6. Liu L, Tuuli MG, Roehl KA, Odibo AO, Macones GA, Cahill AG. Electronic fetal monitoring patterns associated with respiratory morbidity in term neonates. Am J Obstet Gynecol. 2015;213:681.e681–686.
7. Cahill AG, Tuuli MG, Stout MJ, López JD, Macones GA. A prospective cohort study of fetal heart rate monitoring: deceleration area is predictive of fetal acidemia. Am J Obstet Gynecol. 2018;218:523.e521–523.e512.
8. Triebwasser JE, Colvin R, Macones GA, Cahill AG. Nonreassuring fetal status in the second stage of labor: fetal monitoring features and association with neonatal outcomes. Am J Perinatol. 2016;33:665–70.
9. Lear CA, Galinsky R, Wassink G, Mitchell CJ, Davidson JO, Westgate JA, et al. Sympathetic neural activation does not mediate heart rate variability during repeated brief umbilical cord occlusions in near-term fetal sheep. J Physiol. 2016;594:1265–77.
10. Shaw CJ, Allison BJ, Itani N, Botting KJ, Niu Y, Lees CC, et al. Altered autonomic control of heart rate variability in the chronically hypoxic fetus. J Physiol. 2018;596:6105–19.
11. D'Alton ME, Hankins GDV, Berkowitz RL, Bienstock J, Ghidini A, Goldsmith J, et al. Executive summary: neonatal encephalopathy and neurologic outcome, second edition. Report of the American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy. Obstet Gynecol. 2014;123:896–901.

12. Westgate JA, Bennet L, Gunn AJ. Fetal seizures causing increased heart rate variability during terminal fetal hypoxia. Am J Obstet Gynecol. 1999;181:765–6.
13. Tuuli MG, Stout MJ, Shanks A, Odibo AO, Macones GA, Cahill AG. Umbilical cord arterial lactate compared with pH for predicting neonatal morbidity at term. Obstet Gynecol. 2014;124:756–61.
14. Tuuli MG, Stout MJ, Macones GA, Cahill AG. Umbilical cord venous lactate for predicting arterial lactic acidemia and neonatal morbidity at term. Obstet Gynecol. 2016;127:674–80.
15. Raghuraman N, Temming LA, Stout MJ, Macones GA, Cahill AG, Tuuli MG. Intrauterine hyperoxemia and risk of neonatal morbidity. Obstet Gynecol. 2017;129:676–82.
16. Iscra F, Gullo A, Biolo G. Bench-to-bedside review: lactate and the lung. Crit Care. 2002;6:327–9.
17. Evans CL, Hsu FY, Kosaka T. Utilization of blood sugar and formation of lactic acid by the lungs. J Physiol. 1934;82:41–61.
18. Rochester DF, Wichern WA, Fritts HW, Caldwell PR, Lewis ML, Giuntini C, et al. Arteriovenous differences of lactate and pyruvate across healthy and diseased human lung. Am Rev Respir Dis. 1973;107:442–8.
19. MIitchell AM, Cournand A. The fate of circulating lactic acid in the human lung. J Clin Investig. 1955;34:471–6.
20. Harris P, Bailey T, Bateman M, Fitzgerald MG, Gloster J, Harris EA, et al. Lactate, pyruvate, glucose, and free fatty acid in mixed venosu and arterial blood. J Appl Physiol. 1963;18:933–6.
21. Bellomo R, Kellum JA, Pinsky MR. Transvisceral lactate fluxes during early endotoxemia. Chest. 1996;110:198–204.
22. De Backer D, Creteur J, Zhang H, Norrenberg M, Vincent JL. Lactate production by the lungs in acute lung injury. Am J Respir Crit Care Med. 1997;156:1099–104.
23. Brown SD, Clark C, Gutierrez G. Pulmonary lactate release in patients with sepsis and the adult respiratory distress syndrome. J Crit Care. 1996;11:2–8.
24. Deshpande SA, Platt MP. Association between blood lactate and acid-base status and mortality in ventilated babies. Arch Dis Child Fetal Neonatal Ed. 1997;76:F15–20.
25. Beca JP, Scopes JW. Serial determinations of blood lactate in respiratory distress syndrome. Arch Dis Child. 1972;47:550–7.
26. Clark SL, Nageotte MP, Garite TJ, Freeman RK, Miller DA, Simpson KR, et al. Intrapartum management of category II fetal heart rate tracings: towards standardization of care. Am J Obstet Gynecol. 2013;209:89–97.
27. Frey HA, Tuuli MG, Shanks AL, Macones GA, Cahill AG. Interpreting category II fetal heart rate tracings: does meconium matter? Am J Obstet Gynecol. 2014;211:644.e641–648.
28. Downs T, Zlomke E. Fetal heart rate pattern notification guidelines and suggested management algorithm for intrapartum electronic fetal heart rate monitoring. Perm J. 2007;11:22–28.