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Original article

Category II non-reassuring fetal heart rate pattern and risk of admission to Neonatal Intensive Care Unit

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Abstract

Background: The relationship between non-reassuring fetal heart rate (FHR) pattern, acidemia at birth and neonatal morbidity remains unclear. Our aim was to compare low versus high pH cord blood infants of women detected with a Category II FHR pattern for which the impact is unclear.

Methods: A prospective study of 185 low-risk pregnant women in labor at > $37^{0/7}$ weeks of gestation with a singleton fetus was conducted at a single center. Category II trace was defined by the presence of tachycardia or bradycardia, variable and late decelerations, marked variability at least 30 minutes in the 120 minutes prior to delivery. The primary outcome included the need for resuscitation and Neonatal Intensive Care Unit (NICU) admission. The cohort was also stratified into three categories according to admission to NICU and pH threshold ([i] umbilical artery blood pH < 7.15 and admitted; [ii] pH > 7.15 and admitted; [iii] not admitted).

Results: 23% (43/185) of infants of women detected with Category II FHR pattern needed NICU admission. Category II FHR pattern was associated with low pH at birth, and the need for resuscitation was more frequent among infants in the lower pH group (73% vs. 10%, $p < 0.05$). Indices of right (tricuspid annular plane systolic excursion [TAPSE]: 7.3 ± 0.9 mm) and left ventricular performance (fractional shortening: 31% ± 8.9%, transmitral E'/A' 0.9 ± 0.3) were low compared to normative data for healthy infants. CK, CK-MB, and left-to-right/bidirectional shunts at PFO and PDA were higher overall at 72 hours of age.

Conclusions: Category II FHR is associated with resuscitation at birth, NICU admission, and length of hospitalization.

Keywords

Acidemia, electronic fetal monitoring, neonatal morbidities, term infants, myocardial performance, neonatal intensive care.

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Introduction

When first introduced, electronic fetal heart rate (FHR) monitoring was used primarily for complicated pregnancies. Over time it became a standard of care intervention, so by 1978 nearly two-thirds of American women were monitored electronically during labor [1]. At the same time, an expert panel concluded that increased use of electronic monitoring in complicated pregnancies was linked to more frequent cesarean delivery, but the improvement in neonatal outcomes was marginal. While a detailed description of the electronic FHR physiology is beyond the scope of this article, the latest intrapartum cardiotocography FIGO classification system is described elsewhere (**Tab. 1**) [2, 3]. Category I and III patterns are easy to define and prompt a binary response to either "not intervene" or "deliver now". Category II, however, represents an intermediary pattern of "presumed increased risk", based on the likelihood of neonatal asphyxia. The negative predictive value of Category I pattern (99.2%) for fetal acidemia (pH < 7.1) was previously demonstrated by Cahill et al. [4]. In addition, the presence of recurrent decelerations worsens fetal acidemia due to myocardial impairment and reduced fetal cardiac output [5]. Category II traces are seen in over 80% of laboring women but prior attempts to define the relation between cardiotocography parameters [4] or temporal effect of the pattern on neonatal outcomes have failed to define a safe limit for fetuses at risk of asphyxia [6]. Toomey and Oppenheimer demonstrated antenatal tachycardia to be the most sensitive predictor of neonatal acidemia (pH < 7.15), compared to late or total deceleration, for low risk singleton pregnancy where a Category II pattern is detected [7]. Acidemia at the time of birth is a risk factor for neonatal morbidity, including neurologic injury and mortality [8, 9]. Numerous studies have assessed the relationship between electronic FHR pattern and neonatal outcome, but there are limited data on cardiovascular outcomes [10, 11]. Giesinger et al. recently demonstrated, in a cohort of asphyxiated infants undergoing therapeutic hypothermia, that impaired right ventricular (RV) function predicted the composite outcome of death and brain injury [12]. There are no studies investigating the relationship between infants with borderline concern for asphyxia and impaired cardiac performance in newborns. The goal of our study was to compare the neonatal outcomes of low versus high cord blood pH of infants birthed of women detected with Category II electronic FHR monitoring pattern. We hypothesized that Category II electronic FHR monitoring pattern and acidemia (cord pH < 7.15) will be associated with increased neonatal morbidity in term infants.

Table 1. Intrapartum cardiotocography FIGO classification system [2, 3].

	Category I	Category II	Category III
Baseline	110-160 bpm	Lacking at least one characteristic of normality, but with no pathological features	< 100 bpm
Variability	5-25 bpm	Lacking one characteristic of normality, but with no pathological features	Low/higher variability, or sinusoidal pattern
Decelerations	No repetitive decelerations	Lacking at least one characteristic of normality, but with no pathological features	Repetitive late or pro-longed decelerations during > 30 min or 20 min if reduced variability, or one prolonged deceleration with > 5 min
Clinical care	No intervention necessary to improve fetal oxygenation state	Action to correct reversible causes if identified, close monitoring or additional methods to evaluate fetal oxygenation	Immediate action to correct reversible causes, additional methods to evaluate fetal oxygenation, or if this is not possible expedite delivery
Interpretation	Fetus with no hypoxia/acidosis	Fetus with a low probability of having hypoxia/acidosis	Fetus with a high probability of having hypoxia/acidosis

Methods

This was a prospective observational study, performed between July 2018 and July 2019, at University County Hospital Tirgu Mures, Romania. The study received *a priori* approval by the institutional Ethics Committee, and consent was obtained from the parent or guardian of all participants. Eligible criteria included continuous electronic FHR monitoring for 2 hours before delivery, birth after uncomplicated low-risk pregnancies. Evolutive measurements time points are presented in **Fig. 1**.

Inclusion criteria

Neonates were enrolled in the study if they fulfilled the following criteria:

a. gestational age between 37 and 42 weeks;
b. postnatal age < 24 hours;
c. established diagnosis of Category II non-reassuring FHR defined as follows: baseline rate < 110 or/and > 160 bpm; moderate FHR variability; presence or absence of acceleration, absence of late or variable decelerations, presence or absence of early decelerations.

Exclusion criteria

a. Severe fetal acidemia defined by pH < 7.0;
b. antenatal diagnosis of congenital heart disease;
c. alternative diagnosis for altered biochemical markers or echo parameters;
d. central nervous system malformations;
e. intrauterine growth retardation;
f. *in utero* infection.

Outcomes

The primary outcome was the need for stabilization after birth and Neonatal Intensive Care Unit (NICU) admission. The secondary outcomes included cardiac performance evaluated at 72 hours of age assessed by echocardiography. For those infants who needed NICU admission, a cut-off value of 7.15 for pH was chosen according to recent evidence suggesting a role for therapeutic hypothermia use in infants with arterial pH between 7.1 and 7.15 [13].

Clinical data

We collected maternal data including age, education, residency, tobacco use during pregnancy, antenatal care visits, gestational hypertension, parity, and latency interval (defined as the interval of time in hours from membrane rupture to delivery). The continuous electronic FHR tracings were recorded with a Comen STAR5000F monitoring machine (Shenzen Comen Medical Instruments Co.Ltd.) and analyzed by visual observation. Variables related to labor included: mode of delivery (vaginal or cesarean delivery), operative delivery (vacuum-assisted), fetal presentation, nuchal cord, and presence of meconium-stained fluid. Neonatal clinical information included gender, birth weight, Apgar scores at 1 and 5 minutes. The illness severity score (SNAPPE-II) was calculated at 24 hours of age [14]. Small and large for gestational age (SGA and LGA) were defined as neonatal weight under the 10th or over the 90th percentiles, respectively [15]. All deliveries were attended by one neonatologist and one advanced nurse trained in Neonatal Resuscitation Program (NRP). Resuscitation at birth was provided to non-vigorous neonates defined by the presence of one or more of the following features at birth: apnea/gasping breathing, heart rate < 100/min, poor muscle tone. Newborns were resuscitated in the delivery room as per the American Academy of Pediatrics (2010) NRP Guidelines. Resuscitation in the delivery room was initiated manually with bag and face mask, followed by endotracheal intubation if respiratory depression continues. The decision for admission to the NICU was at the discretion of the attending neonatologist.

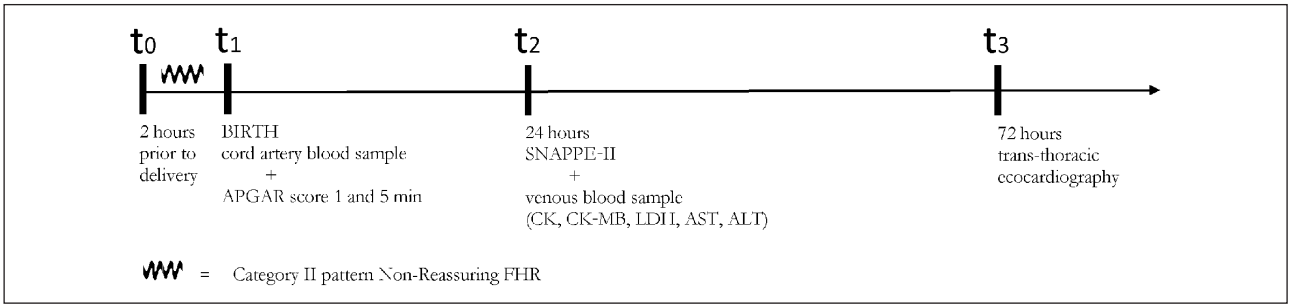

Figure 1. Evolutive measurements time points.
CK: creatine kinase; CK-MB: creatine kinase-MB isoenzyme; FHR: fetal heart rate; LDH: lactate dehydrogenase.

Respiratory support during NICU stay was defined as any positive pressure support provided for those infants with apnea or bradycardia who failed to respond to basic resuscitation measures into the delivery room. Total length of stay in the NICU/ hospital was also recorded.

Biochemical markers

Umbilical artery pH was sampled in a pre-heparinized syringe after cord clamping and within 3 minutes of birth. The blood sample was analyzed by a blood gas analyzer in the delivery room (ABL 800 flex, Radiometer, France). Serum creatine kinase (CK), creatine kinase-MB isoenzyme (CK-MB), and lactate dehydrogenase (LDH) were measured from venous blood samples at 24 hours of age. CK and CK-MB activities were measured according to their electrophoretic mobility on agarose gel. LDH activity was measured with the LDH-P test. Values were expressed in μg/l and IU/l at 15-30 grades Celsius [16, 17].

Echocardiography

Comprehensive trans-thoracic echocardiography, according to a standardized protocol, was performed at 72-hours on a Philips® ultrasound scanner with a 10 MHz transducer (Philips® EPIQ CvX). All assessments were performed by a single experienced sonographer (A.F.) who was blind to the clinical condition of enrolled patients or treatments provided. In addition, the medical team remained blinded to the echo results. Conventional measurements were obtained according to the guidelines of the American Society of Echocardiography [18, 19]. Specific methodological details of the assessment of right and left ventricular (LV) systolic and diastolic performance, as well as indices of ventricular dimensions and function, are provided in **Tab. 2**.

Table 2. Echocardiographic indices of ventricular dimensions and function.

	Echo window	Description
RV systolic performance		
Tricuspid valve inflow	Apical RV-4C view	Assessed by placing a pulsed-wave sample gate of 2 mm at the tip of the tricuspid valve leaflets during diastole with the Doppler beam parallel to the inflow as visualized using color Doppler. Early TvE and late TvA inflow velocity and ratio TvE:TvA
TAPSE (M-mode)	Apical RV-4C view	A linear measurement of the maximum displacement of the tricuspid annulus during each contraction, obtained placing the cursor thorough the lateral aspect of tricuspid annulus while maintaining vertical alignment with apex
LV dimensions		
MAPSE (M-mode)	Apical LV-4C view	A linear measurement of the maximum displacement of the mitral annulus during each contraction, obtained placing the cursor thorough the lateral aspect of mitral annulus while maintaining vertical alignment with apex
LVIDd **LVIDs** **LVPW**	M-mode of the long axis	LVIDd – Inner edge to inner edge, perpendicular to the long axis of the left ventricle, at or immediately below the level of the mitral valve leaflet tips. Performed at end-diastole (the frame with the largest LV dimensions/volume) LVIDs – Inner edge to inner edge, perpendicular to the long axis of the left ventricle, at or immediately below the level of the mitral valve leaflet tips. Performed at end-systole (the frame with the smallest LV dimensions/volume) LVPWd maximum posterior excursion defines end-diastole LVPWs maximum anterior excursion defines end-systole
LV systolic performance		
FS	Parasternal short axis view	M-mode derived FS – Systolic function based from LV dimensions
EF	Apical 4C view	B-mode derived using Simpson's bi-plane method based from LV dimensions
Myocardial TDI		
Peak systolic S' **Early diastolic E'** **Late diastolic A'**	Apical 4C view	A pulsed wave Doppler sample placed at the base of wall to minimize the angle of isonation to less than 20 degrees
Transitional shunts		
Atrial septum **PFO** **PDA**	Subcostal view Parasternal view (High)	2D or spectral color flow Doppler B-mode and pulsed wave Doppler The shunt pattern was classified as shunting from systemic to pulmonary circulation (left-to-right), from pulmonary to systemic circulation (right-to-left) or bidirectional

EF: ejection fraction; FS: fractional shortening; LV: left ventricle; LVIDd: left ventricle internal diameter diastole; LVIDs: left ventricle internal diameter systole; LVPW: left ventricle posterior wall; MAPSE: mitral annular plane systolic excursion; PDA: patent ductus arteriosus; PFO: patent foramen ovale; RV: right ventricle; TAPSE: tricuspid annular plane systolic excursion; TDI: tissue Doppler imaging.

For each measurement, 3 to 5 consecutive cardiac cycles were recorded. Each measurement was averaged from 3 representable measurements to minimize the effect of biological and random variation. Middle cerebral artery (MCA) resistive index (RI) was also measured at the time of echocardiography studies assessment. Settings were optimized for cranial ultrasound. Doppler measurements were taken parallel to the line of MCA flow. RI was calculated using the formula: [Systolic Vmax (cm/sec) - Diastolic Vmax (cm/sec)]/Systolic Vmax (cm/sec), where Vmax refers to peak velocity [21].

Statistical analysis

For this 1-year study period, a convenience sample size was chosen as this study was considered hypothesis-generating. Each mother-infant dyad was considered a case. Data were recorded on a Microsoft® Excel® spreadsheet and analyzed using SPSS® statistical software. Descriptive statistics were used to test continuous variables for normality. Mean with standard deviation or median with interquartile range were used for normal vs. non-normal distribution, respectively. Univariate analysis using the Student's t-test or the Mann-Whitney U test were used as appropriate to determine intergroup differences between those with acidemia (pH < 7.15) and those without acidemia (pH ≥ 7.15) based on dependent variables. ANOVA was conducted to compare both groups with patients who had a Category II trace but were not admitted to the hospital. Categorical variables were presented as frequencies (%) and compared using the Chi-square test or Fisher's exact test. Results were considered significant if $p < 0.05$. All analyses were performed using software (SAS®, Version 9.4 for Windows®; SAS Institute Inc, Cary, NC).

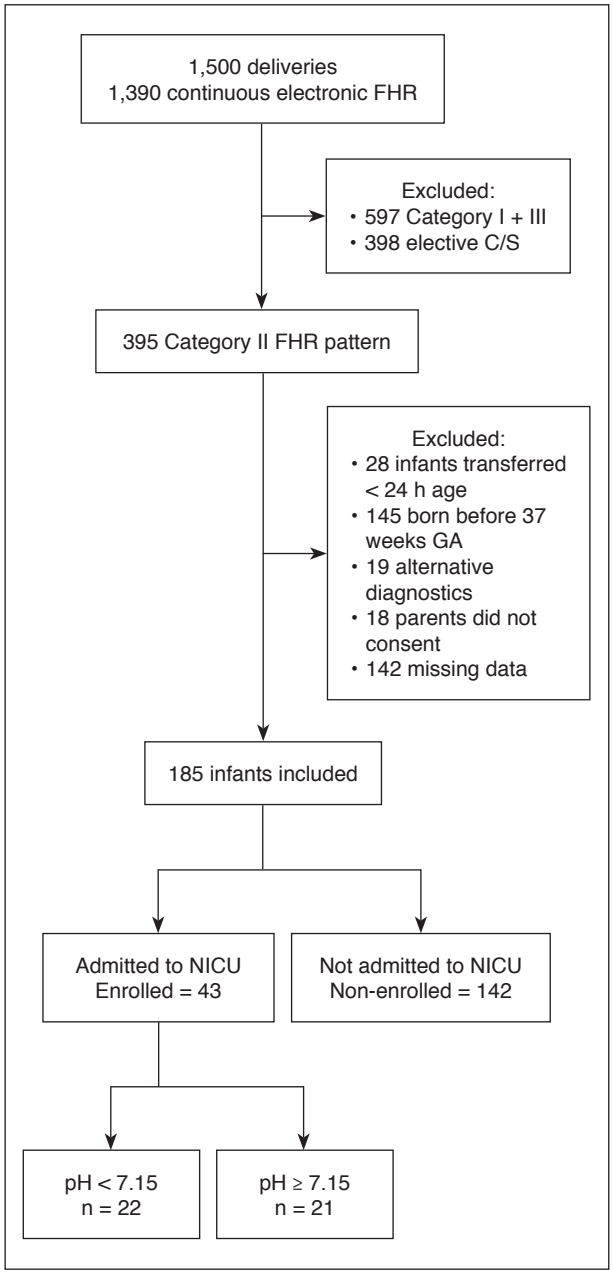

Figure 2. 1,500 eligible deliveries were screened, of whom 1,390 (92%) had continuous electronic fetal heart rate (FHR) monitoring during labor.

C/S: cesarean section; FHR: fetal heart rate; NICU: Neonatal Intensive Care Unit.

Results

We screened 1,500 eligible deliveries, of whom 1,390 (92%) had continuous electronic FHR monitoring during labor (**Fig. 2**). Among these, 597 (43%) were classified as Category I and III, and 398 (28.5%) were elective cesarean delivery (previous cesarean section or other medical or obstetric indications); 395 (28%) cases were identified as Category II electronic FHR tracing. Of the latter Category, 145 (36%) infants were born preterm before 37 week's gestation, and 28 (7%) infants were transferred, within 24 hours of birth, to tertiary referral centers for illnesses that required surgical or subspecialty care. Of the remaining 185 infants who satisfied eligibility criteria and were admitted to the NICU, 43 (22.8%) were enrolled and sub-categorized according to blood pH < 7.15 (n = 22) or ≥ 7.15 (n = 21). The remaining eligible 142 infants, not admitted to NICU, were categorized as the non-enrolled group.

Maternal characteristics

Baseline maternal demographics were comparable between all groups, although mothers in the non-

enrolled group had a lower rate of antenatal visits (**Tab. 3**). Maternal hypertension was more frequent among cases with pH < 7.15 compared with non-enrolled (9% vs. 1%, p = 0.03) patients. Among enrolled cases, over half (60%) cases were born by cesarean delivery after a course of labor. Non-enrolled patients were more likely to be born by spontaneous vaginal delivery. Enrolled patients were more likely to have nuchal cord, presence of meconium-stained amniotic fluid, and prolonged rupture of membranes.

Neonatal characteristics

Mean birth weight and gestational were comparable between pH subgroups, but higher than in non-enrolled infants (**Tab. 4**). The rate of LGA were highest among enrolled infants with lower cord pH. There was an increased need for resuscitation at birth in the low pH group (16/22 [73%] vs. 2/21 [10%], p < 0.001); however, the need for respiratory support did not differ between groups (5/22 [23%] vs. 3/21 [14%], p > 0.05). Interestingly, the SNAPPE-II score at 24 hours was higher for infants in the higher pH group (21 ± 1.9 vs. 26 ± 2.9, p < 0.001). Median serum CK concentration was higher among enrolled vs. non-enrolled infants. A marginal difference between all groups was found for elevated ALT level, but no difference in AST, LDH, and creatinine at 24 hours was noted. Among enrolled infants, the length of NICU stay was highest in the low pH group (5.9 ± 2.5 vs. 3.2 ± 0.4, p < 0.001).

Cardiovascular performance

Overall, we found no statistical difference in indices of RV/LV systolic performance between the low vs. high pH group (**Tab. 5**). While tricuspid annular plane systolic excursion (TAPSE) was not different between low and high pH groups (7.2 ± 0.6 vs. 7.3 ± 1.1, p > 0.05), values were 25-30% lower than published normative data for RV systolic function. The rate of left-to-right transatrial, but not transductal, shunting was higher in the low pH group (10/12 vs. 12/16, p = 0.01). There was no case of neonatal hypothyroidism, which may impact transitional cardiovascular physiology.

Discussion

Our findings are clinically relevant as 85% of live births were assessed with continuous FHR, making it the most common obstetric procedure [22]. Previous studies have highlighted the value of continuous electronic FHR in screening for fetal cardiovascular health. Toomey and Oppenheimer demonstrated the value of fetal tachycardia as a screening tool for neonatal acidosis [7]. In our population of women with low-risk pregnancies, as adjudicated by a Category II FHR tracing, 23% of newborns developed adverse neonatal outcomes, of whom half had cord blood pH at birth less than 7.15. The threshold of 7.15 was chosen based on recent evidence that suggests a beneficial effect of therapeutic hypothermia for infants with arterial pH ranging from 7.1 and 7.15 [13].

Table 3. Demographics of the mothers and obstetric characteristics.

		pH < 7.15 (n = 22)	pH ≥ 7.15 (n = 21)	Non-enrolled (n = 142)	p-value
Maternal age, years		25.7 ± 7.8	27.9 ± 7.7	26.6 ± 7.2	ns
Urban residency, n (%)		9 (41)	7 (33)	61 (43)	ns
Maternal education, years		8.1 ± 4	9.0 ± 3.5	8.0 ± 4.4	ns
Smoking during pregnancy, n (%)		8 (36)	9 (43)	40 (28)	ns
Married, n (%)		8 (36)	12 (57)	67 (47)	ns
Antenatal care visits, n (%)		21 (96)	20 (95)	18 (13)	< 0.001 [c, b]
Parity	**1**	9 (41)	9 (43)	51 (36)	ns
	2	4 (18)	2 (10)	22 (16)	
	3+	9 (41)	10 (47)	69 (49)	
Spontaneous vaginal delivery, n (%)		6 (27)	11 (52)	82 (58)	0.03 [c]
Operative vaginal, n (%)		6 (27)	8 (38)	32 (23)	ns
Fetal presentation cephalic, n (%)		22 (96)	19 (95)	135 (95)	ns
Nuchal cord, n (%)		7 (32)	8 (38)	20 (14)	0.008 [d, b]
Meconium stained fluid, n (%)		6 (27)	7 (33)	4 (3)	< 0.001 [c, b]
Latency interval in case of PROM, hours		1 [0, 4]	3 [4, 12]	1 [0, 5.3]	0.03 [a, b]
Maternal hypertension, n (%)		2 (9)	1 (5)	1 (1)	0.03 [c]

Data are expressed as mean (SD), or number (percentage), as appropriate.
[a] p < 0.05 between pH < 7.15 and pH ≥ 7.15; [b] p < 0.05 between pH ≥ 7.15 and non-enrolled; [c] p < 0.05 between pH < 7.15 and non-enrolled; [d] p < 0.1 between pH < 7.15 and non-enrolled.
ns: not significant; PROM: prolonged rupture of membranes.

Table 4. Neonatal birth demographics, postnatal characteristics and perinatal interventions.

	pH < 7.15 (n = 22)	pH ≥ 7.15 (n = 21)	Non-enrolled (n = 142)	p-value
Birth weight, kg	3,328 ± 543	3,293 ± 636	2,994 ± 574	0.008 [c, e]
Gestational age, weeks	38.9 ± 1.3	39.8 ± 1.8	38.1 ± 1.7	< 0.001 [b]
Male sex, n (%)	11 (50)	11 (52)	74 (52)	ns
Head circumference, cm	33.7 ± 2.6	33.6 ± 1.7	32.8 ± 1.8	0.02 [d]
Length, cm	52.0 ± 2.9	52.1 ± 3.0	50.8 ± 3.2	0.07
AGA, n (%)	14 (64)	14 (67)	104 (73)	ns
SGA, n (%)	4 (18)	5 (24)	38 (27)	ns
LGA, n (%)	4 (18)	2 (10)	0	< 0.001 [c, b]
Apgar score < 7 (1 min), n (%)	11 (50)	7 (33)	5 (4)	< 0.001 [c, b]
Apgar score < 7 (5 min), n (%)	1 (5)	1 (5)	0	0.04
Cord arterial blood pH	7.10 ± 0.04	7.25 ± 0.06	7.27 ± 0.09	< 0.001 [a, c]
Resuscitation at birth, n (%)	16 (73)	2 (10)	0	< 0.001
Respiratory support, n (%)	5 (23)	3 (14)	0	ns
SNAPPE-II score at 24 hours	21 ± 1.9	26 ± 2.9	n/a	< 0.001
CK, *μ*g/l	849 [486, 1,487]	781 [362, 1,018]	540 [405, 868]	0.018 [a, c]
CK-MB, *μ*g/l	76 [58, 133]	79 [61, 91]	61 [44, 86]	ns
LDH, mmol/l	1,013 [769, 1,463]	1,055 [800, 1,553]	944 [516, 1,231]	ns
AST, IU/l	64 [47, 81]	73 [49, 88]	54 [40, 74]	ns
ALT, IU/l	23 [15, 42]	21 [17, 34]	14 [9, 26]	0.049 [b, c]
Creatinine	0.8 ± 0.19	0.8 ± 0.2	0.72 ± 0.09	ns
Length NICU stay, days	5.9 ± 2.5	3.2 ± 0.4	0	< 0.001
Length hospital stay, days	6.8 ± 2.5	5.9 ± 1.8	5.8 ± 3.1	ns

Data are expressed as mean (SD), or number (percentage), as appropriate.
[a] p < 0.05 between pH < 7.15 and pH ≥ 7.15; [b] p < 0.05 between pH ≥ 7.15 and non-enrolled; [c] p < 0.05 between pH < 7.15 and non-enrolled; [d] p < 0.1 between pH < 7.15 and non-enrolled; [e] p < 0.1 between pH ≥ 7.15 and non-enrolled.
AGA: appropriate for gestational age; CK: creatine kinase; CK-MB: creatine kinase-MB isoenzyme; LDH: lactate dehydrogenase; LGA: large for gestational age; NICU: Neonatal Intensive Care Unit; ns: not significant; SGA: small for gestational age.

Table 5. Echocardiography indices of myocardial performance.

	pH < 7.15 (n = 22)	pH ≥ 7.15 (n = 21)	All (n = 43)	p-value	Normative data for healthy term
RV functional indices					
Tricuspid E, m/sec	0.64 ± 0.04	0.72 ± 0.06	0.68 ± 0.06	ns	0.44 ± 0.07
Tricuspid A, m/sec	0.67 ± 0.08	0.54 ± 0.1	0.51 ± 0.01	ns	0.53 ± 0.08
Tricuspid E/A	0.81 ± 0.1	0.83 ± 0.1	0.82 ± 0.01	ns	0.83 ± 0.01
TAPSE, mm	7.2 ± 0.6	7.3 ± 1.1	7.3 ± 0.9	ns	9.1 ± 0.01
Measurements of RV diastolic performance					
E', cm/sec	6.8 ± 1.4	6.7 ± 1.5	6.7 ± 1.5	ns	7.3 ± 1.2
A', cm/sec	7.6 ± 1.5	7.6 ± 1.8	7.6 ± 1.7	ns	8.1 ± 1.2
S', cm/sec	6.1 ± 1.4	6.5 ± 1.1	6.4 ± 1.3	ns	6.5 ± 1.1
Measurements of LV diastolic performance					
LV lateral wall E'/A'	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	ns	1.3 ± 0.4
LV lateral E/E'	9.2 ± 3.4	8.4 ± 2.6	8.7 ± 3.1	ns	8.9 ± 2.8
LV functional indices					
Mitral E, m/sec	0.58 ± 0.1	0.57 ± 0.02	0.58 ± 0.15	ns	0. 55 ± 0.08
Mitral A, m/sec	0.63 ± 0.1	0.61 ± 0.01	0.62 ± 0.14	ns	0.49 ± 0.09
Mitral E/A	0.95 ± 0.3	0.97 ± 0.02	0.96 ± 0.26	ns	0.12 ± 0.03
SF, %	35.2 ± 7.1	38.6 ± 10.1	34.1 ± 8.9	ns	39 ± 8
EF, %	58.2 ± 6.6	61.1 ± 8.2	59.6 ± 7.5	ns	65 ± 8
MAPSE, mm	6.7 ± 1.4	7.1 ± 1.1	6.8 ± 1.2	ns	5.6 ± 0.08
Shunts					
PFO LR/BD	10/12	12/16	22/43 (51%)	0.01	80% at 24 h
PFO no flow	10/22	5/21	15/43 (35%)	ns	26% at 35 h
PDA LR/BD	2/3	4/6	6/43 (14%)	ns	33% at 24 h
PDA closed	19/22	15/21	34/43 (79%)	ns	95% at 35 h
MCA RI	0.6 ± 0.2	0.6 ± 0.1	0.6 ± 0.1	ns	0.72 ± 0.4

Data are expressed as mean ± SD, or number (percentage), as appropriate.
A': late diastolic atrial contraction wave; E': early diastolic wave; E/E': pulsed MV E/E' of pulsed tissue Doppler of lateral annulus; EF: ejection fraction; LR/BD: left-to-right/bidirectional; LV: left ventricular; MAPSE: mitral annular plane systolic excursion; MCA: middle cerebral artery; MV: mitral valve; ns: not significant; PDA: patent ductus arteriosus; PFO: patent foramen ovale; RI: resistive index; RV: right ventricular; S': positive systolic wave; SF: shortening fraction; TAPSE: tricuspid annular plane systolic excursion.

In our cohort, meconium-stained amniotic fluid was present in one of four infants, suggesting that meconium presence may indicate low fetal cardiopulmonary reserve. The significance of meconium-stained amniotic fluid is controversial; several studies found no association between the presence of meconium and hypoxia or low Apgar scores [23], while other investigators reported that higher grade meconium was associated with poor obstetrical outcomes and hypoxic-ischemic encephalopathy [24]. In addition, the group of infants with low pH had a higher rate of need for resuscitation at birth compared to those with higher pH. The lack of discordance in need for respiratory support and illness severity during NICU stay between groups most likely relates to the small sample size and the mild nature of illness in this group.

The finding of elevated levels of serum CK, CK-MB, and LDH in the enrolled cohort is noteworthy. Elevated levels of CK and CK-MB are frequently reported in newborns with perinatal asphyxia and myocardial dysfunction and are sensitive markers of subsequent cardiac recovery and mortality [25-26]. The association between elevated level of intracellular cardiac enzymes and low pH at birth has been previously reported; specifically, Nakajima et al. showed that higher level of intracellular enzymes positively correlate with low cord blood pH at birth and are useful predictors of length of respiratory support for those asphyxiated term newborns [26]. The clinical relevance of primary myocardial damage in the setting of HIE has recently been demonstrated [27]; specifically, myocardial dysfunction was reported to be a strong and independent predictor of brain injury and mortality, after adjustment for severity of HIE, despite receipt of therapeutic hypothermia [12, 27].

TAPSE is a simple and reliable measure of RV function, due to the predominant longitudinal nature of myocardial deformation [28, 31]. In adults with pulmonary arterial hypertension, low TAPSE has been shown to correlate with adverse outcomes such as RV remodeling and severity of pulmonary vascular resistance [29]. In neonates with pulmonary hypertension, TAPSE < 6 was a strong predictor of death or need for ECMO (sensitivity 83% and specificity 74%) [30]. The mean TAPSE level in our cohort is lower than published normative data for health term infants [28, 30]. A recent study by Giesinger et al. demonstrated that moderate-severe RV dysfunction predicts increased risk of composite outcome of mortality and/or brain injuries, independent of severity of HIE or illness severity [12]. In addition, the finding of lower values for markers of right and left diastolic function (E'/A') is also noteworthy [30, 32]. We showed that half of the enrolled infants continued to have a patent ductus arteriosus (PDA) opened at 72 postnatal hours, which is unexpected in healthy term neonates after 10-15 hours of age [30, 36, 37]. Alternative explanations for delayed PDA closure include neonatal hypothyroidisim or high altitude, however neither were relevant in our cohort. We speculate that right-to-left or bidirectional shunting across patent foramen ovale (PFO) and PDA was caused by increased right-side pressures during the first 72 hours of age, although we do not have sequential echocardiography data to confirm this hypothesis.

This study highlights two important clinically relevant findings regarding infants born to mothers with low-risk pregnancies detected with Category II FHR pattern. First, the study population is at increased risk of need for resuscitation, stabilization, and NICU admission. Second, the findings of elevated cardiac enzymes and modified ventricular function are suggestive of a more concerning degree of perinatal hypoxia-ischemia, although no patients required anticonvulsants or inotropic support. Unfortunately, we did not perform comprehensive neurologic surveillance with either electroencephalography or brain imaging to appraise neurological risk. Several studies advocate the beneficial effect of therapeutic hypothermia among term infants with moderate-severe HIE less than 6 hours old [12], infants born late preterm with HIE [33], some term infants with HIE more than 6 hours old [34], and following postnatal cardiac arrest in the NICU [35]. Some guidelines suggest screening for additional signs of hypoxia-ischemia when cord blood pH is lower than 7.15, regardless of the degree of antenatal concern [13]. None of the infants included in our study, irrespective of the Category II FHR pattern, fulfilled the criteria for consideration of therapeutic hypothermia. Of concern, several infants demonstrated signs of adverse health and end-organ compromise; specifically, infants in the lower pH group had increased length of NICU stay more than 5 days, consistent with previous reports in the literature [38-42]. Although there were no overt signs of neurological concerns, this should not be interpreted as lack of brain cell injury. It is plausible that there may be neonates with mild, but modifiable, brain injury that is not detectable without a comprehensive neurophysiological appraisal. There is increasing evidence that infants with mild HIE may benefit from therapeutic hypothermia [12, 13, 33-35].

The main limitation in our study is that we did not include a control group, hindering our ability to compare our results findings with a cohort of healthy infants. We compared our findings with previously published data of healthy cohort infants from units with more advanced ultrasound acquisition techniques and expertise in targeted neonatal echocardiography [12, 28, 30, 32, 36, 37, 43]. In addition, we did not perform advanced echocardiography measurements such as strain, and strain rate, which are more sensitive methods to evaluate RV performance [30-32, 41]. The late timing of the echocardiography assessment at 72 hours of postnatal age may have contributed to earlier hemodynamic changes being missed.

Conclusion

In summary, this is the first prospective observational study highlighting the relationship of Category II FHR patterns with neonatal health and myocardial performance. The findings of biochemical evidence of myocardial injury and altered RV performance may be suggestive of increased risk of brain injury. These data should prompt future studies to characterize the magnitude of effect in an appropriately powered sample size and the impact of lower RV function on cerebral hemodynamics, neurophysiology, and brain injury.

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Declaration of interest

Neither of the Authors has any conflicts of interest to declare. Funding: this research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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