

Heart rate variability evaluation in the assessment and management of in-utero drug-exposed infants

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Abstract

Aim: To determine whether heart rate variability parameters vary between in-utero drug-exposed infants and controls. To determine correlations between Finnegan score and heart rate variability parameters. To differentiate those drug-exposed infants who require treatment from those infants who do not.

Methods: A total of 24 jaundiced control subjects and 25 in-utero drug-exposed infants were enrolled. The Finnegan score and an electrocardiographic rhythm strip were obtained at 4-h intervals. RR intervals (time between consecutive R waves) were manually tabulated from the rhythm strip and analyzed. Time-domain heart rate variability parameters were calculated and analyzed for both groups.

Results: Heart rate variability parameters were cumulatively lower over 3 days in in-utero drug-exposed infants compared with controls ($p < 0.05$). Root mean square of differences of standard deviation of RR intervals on first day of life, and standard deviation of RR intervals, percentage of consecutive RR intervals greater than 50ms, and root mean square of differences of standard deviation of RR intervals on the second day of life were significantly lower between in-utero drug-exposed infants and control infants. Three out of five parameters were significantly lower in in-utero drug-exposed infants pre-treatment versus post-treatment ($p = 0.001$, $p = 0.0001$, and $p = 0.021$, respectively). Root mean square of differences of standard deviation of RR intervals was able to differentiate in-utero drug-exposed infants requiring opiate therapy and in-utero drug-exposed infants that did not ($p = 0.02$).

Conclusion: Heart rate variability analysis can contribute to the management of in-utero drug-exposed infants. Heart rate variability could be used in dose titration.

Keywords

Heart rate variability, neonatal abstinence syndrome, Finnegan score

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Introduction

Approximately 3% of the 4.1 million women of childbearing age who abuse illicit drugs are believed to continue drug use during pregnancy in United States.¹ The Centers for Disease Control and Prevention National Vital Statistics in 2009 estimated that 160,000 newborns, or 4% of all live births, in the United States were exposed to illicit drugs during pregnancy. Opioids (naturally occurring, synthetic, and semi-synthetic) are the most frequently detected drugs in infants exposed to drugs in-utero. The incidence of neonatal abstinence syndrome (NAS) ranges from 21% to 94% among in-utero drug-exposed infants (IUDEI).²

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NAS refers to a constellation of signs and symptoms due to drug withdrawal in the neonatal period. In 1975, Dr Loretta Finnegan and associates developed an assessment and treatment protocol for opiate withdrawal in newborns called the Finnegan score. The score is based on observation of 21 clinical withdrawal signs and is repeated at regular intervals. This method is subjective, biased, and time consuming, and insensitive to detecting IUDEI in preterm infants, with a high inter-observer variability.³ However, the autonomic cardiovascular function is not included while using the Finnegan score. The role of the endogenous opioid system in the control of autonomic cardiovascular function is believed to be due to μ -opioid receptors in the hypothalamus.^{4,5}

Heart rate variability (HRV) is a non-invasive index of autonomic activity of the heart.^{6,7} HRV (autonomic nervous system capacity) has been studied in adults, neonates, and fetuses.⁸⁻¹⁰ HRV parameters were also evaluated in neonates with hyperbilirubinemia and were noted to have decreased variability compared to healthy normal newborns.¹¹

Timely treatment of IUDEI can prevent morbidity, including seizures, poor feeding, and poor weight gain.¹² There are no studies that have examined daily time-domain HRV indices and their relation to the Finnegan score within the first 3 days of life in IUDEI. Furthermore, the effect of opioids on HRV in IUDEI is not clear. We compared time-domain HRV parameters among the hyperbilirubinemia patients (more stringent controls) and IUDEI and assessed correlation between HRV parameters and Finnegan score within IUDEI. We further evaluated HRV indices pre- and post-opiate therapies in IUDEI who qualified for treatment.

Methods

Our study was a prospective, observational, pilot study, conducted from December 2011 through November 2012, after Institutional Review Board approval at St John Providence Children's Hospital (1211-05). Consent waiver was obtained because cardiac monitoring is the standard of care for all special-care nursery (SCN) (a step-down unit for observation) patients.

Subjects

A total of 25 full-term IUDEI and 24 full-term hyperbilirubinemic neonates (controls) were included. All cases and controls were admitted to SCN. We chose this control group so that both groups are exposed to same environmental conditions (SCN) that are known to affect HRV parameters.¹³

Our institutional normal practice for IUDEI is to admit to SCN (a step-down unit from neonatal intensive care unit (NICU)) for 3 days for regular Finnegan score assessment that needs special training¹⁴ and requires lower nurse to patient ratio to do rating every 4 h. According to guidelines of perinatal care (7th edition) by American College of Obstetrics and Gynecology (ACOG) and American Academy

of Pediatrics (AAP), urine drug screen is required with a history of maternal drug use, failed screening questionnaire in prenatal visits, unexplained intrauterine growth retardation, abruption placenta, and limited or no prenatal care. In-utero opioid exposure was confirmed either by history and/or positive urine drug screen and the infants qualified for admission to SCN for Finnegan score rating every 4 h (standard of care) for 72 h.

All IUDEI fulfilled the following inclusion criteria: positive in-utero exposure, a 5-min Apgar score of higher than 7 with no other comorbidities that affect HRV, no maternal history of collagen vascular diseases (rule out heart block), no magnesium exposure in perinatal period, with no comorbidities of hyperbilirubinemia or fetal arrhythmias. All IUDEI received meconium drug screen (MDS). MDS is a standardized panel that detects amphetamines, cannabinoids, cocaine, opiates, phencyclidine, methadone, barbiturates, benzodiazepines, and propoxyphene. Any detected drug level was considered positive even if it was below cut value.

Although cocaine withdrawal symptoms are usually insignificant, one patient using cocaine denied drug abuse; so, multidrug abuse could not be ruled out. Another cocaine positive patient was also positive for opioid. Both patients were included.

Control infants were gestational age-, sex- and Apgar score-matched to IUDEI. The control group consisted of term infants admitted to SCN with non-hemolytic indirect hyperbilirubinemia (normal hemoglobin for age, negative Coombs' test, and normal reticulocyte count for age). None of the controls had drug screening performed because none fulfilled previously mentioned indications.

Demographic data (gestational age, race, sex, birth weight, length, and head circumference) were collected for both cases and controls. These data were obtained from neonatal database and electronic medical records.

HRV

Electrocardiographic (EKG) rhythm strips were obtained every 4 h on all IUDEI and control neonates. HRV data were collected over the first 72 h of life; 377 EKG rhythm strips were manually tabulated. Other EKG strips were excluded either due to early discharges (not done) especially for control group or not obtained at the same time as the Finnegan score. The RR intervals were measured manually from the rhythm strip and the corresponding Finnegan score was recorded by registered nursing staff every 4 h as well as the morphine dosage if given.

EKG reviewers were blinded to the two groups. By definition, ARR is an average RR interval, and was calculated by summing all RR intervals and dividing the sum by the number of RR intervals on each EKG strip. SD_{RR} refers to standard deviation of RR intervals on each EKG rhythm strip. Time-domain analysis (the root mean square of differences of standard deviation of RR intervals (RMSSD) and

Table 1. Definitions of time-domain HRV parameters.

HRV parameters	Unit	Definition
RR	Seconds	RR interval in each EKG strip every 4 h
SD_RR	Seconds	SD of RR intervals in each EKG strip every 4 h
RMSSD	Seconds	The square root of the mean of the sum of the squares of differences between adjacent RR intervals
PNN50	Percentage	Percentage of successive RR interval differences >50 ms

HRV: heart rate variability; EKG: electrocardiographic; SD: standard deviation.

the percentage of consecutive RR intervals greater than 50 ms (PNN50)) was performed using guidelines published in 1996.⁶ HRV parameters (Table 1) were analyzed daily and collectively over 3 days.

HRV and opioid therapy

For IUDEI requiring therapy, the AAP guidelines² suggest opioids, barbiturates, and clonidine, either alone or as a combination. IUDEI medical management with morphine was indicated if three or more consecutive Finnegan scores were 8 or higher. Morphine was administered orally at a starting dose of 0.05 mg/kg/dose every 4 h and was titrated based on the Finnegan score. Correlation analysis was done comparing Finnegan scores and HRV parameters pre- and post-morphine treatment.

Statistics

Analysis was performed using Excel spread sheets. T-test and Pearson's correlation were used for analysis, and a p value less than 0.05 was considered statistically significant.

Results

Subjects

We studied 25 IUDEI and 24 infants with hyperbilirubinemia only. There was no statistical difference in the demographic and anthropometric data (Table 2). Maternal urine drug screen was positive in 19 (76%) IUDEI and that included morphine,⁵ hydrocodone,⁶ methadone,⁵ cocaine,¹ cocaine and opioids,¹ and hydromorphone.¹ MDS was positive in 64% (16 out of 25 cases), and the rest was negative.

HRV assessment

Collective 72-h HRV analysis showed that ARR, PNN50, RMSSD, and SD_RR were lower in cases versus controls;

Table 2. Demographics.

Parameters	Cases (mean ± SD)	Controls (mean ± SD)	p value
Number	25	24	
Gender	13 M/12 F	9 M/15 F	0.39
Race	19 White 6 Black	16 White 6 Black 2 Asian	0.32
Gestational age (weeks)	38.2 ± 1.2	38.4 ± 1.2	0.61
Birth weight (kg)	2.88 ± 0.57	3.08 ± 0.55	0.2
Length (cm)	48.8 ± 3	49.6 ± 2.68	0.36
Head circumference (cm)	33 ± 2	33.5 ± 1.6	0.41

SD: standard deviation.

the average heart rate (AHR) was higher among the cases (Table 3). All parameters, except PNN50, were significantly different between the groups ($p < 0.05$). Daily analyses were subsequently performed and showed the following: Day 1—only RMSSD was significantly lower ($p=0.04$) in cases than in controls; Day 2—RMSSD, SD_RR, and PNN50 were significantly lower in IUDEI ($p=0.003$, $p=0.002$, and $p=0.04$, respectively) than the controls; Day 3—no significant difference between the controls and cases was noted (Table 4).

HRV and Finnegan score

There exists a weak positive correlation between Finnegan scores and mean heart rate ($p=0.001$) and a weak negative correlation with ARR and SD_RR, $p=0.0001$ and $p=0.023$, respectively (Table 5). Correlation studies performed on daily HRV parameters and respective Finnegan scores showed a strong negative correlation with SD_RR and RMSSD ($r=-0.85$, $p=0.03$ and $r=-0.9$, $p=0.01$, respectively) only on the third day of life (Table 6). RMSSD was able to differentiate IUDEI with Finnegan score greater than or equal to 8 from IUDEI with Finnegan score less than 8 ($p=0.02$).

HRV and opioid therapy

Six neonates met the treatment criteria and received morphine therapy. SD_RR, RMSSD, and PNN50 were significantly lower in IUDEI pre-treatment versus post-treatment ($p=0.001$, $p=0.0001$, and $p=0.021$, respectively). There was a trend toward lower ARR in pre-treatment patients versus post-treatment. ($p=0.07$, Figure 1).

Discussion

HRV measurement is an objective method, unlike the Finnegan score. The subjectivity of the Finnegan score is based on the individual rater of clinical symptoms resulting

Table 3. HRV parameters over 72 h.

Parameters	Cases	Controls	p value
AHR (BPM)	142.1 ± 17.3	135.7 ± 17.8	0.001
ARR (s)	0.43 ± 0.06	0.45 ± 0.07	0.001
SD_RR	0.01 ± 0.02	0.08 ± 0.31	0.032
PNN50	1.34 ± 3.9	1.97 ± 4.6	0.183
RMSSD	0.01 ± 0.01	0.02 ± 0.04	<0.001

HRV: heart rate variability; AHR: average heart rate; BPM: beats per minute; ARR: average RR intervals; SD_RR: standard deviation of RR intervals; PNN50: percentage of consecutive RR intervals greater than 50 ms; RMSSD: root mean square of differences of standard deviation of RR intervals.

Table 4. HRV parameters by days.

Parameters	Cases	Controls	p value
Day 1			
AHR (BPM)	139.2 ± 10.6	135.5 ± 13.9	0.32
ARR (s)	0.43 ± 0.03	0.45 ± 0.06	0.34
SD_RR	0.01 ± 0.01	0.09 ± 0.3	0.28
PNN50	1.23 ± 2.4	1.7 ± 2.1	0.43
RMSSD	0.01 ± 0.007	0.1 ± 0.016	0.04
Day 2			
AHR (BPM)	143.1 ± 14	140.7 ± 24	0.78
ARR (s)	0.42 ± 0.04	0.43 ± 0.06	0.74
SD_RR	0.01 ± 0.009	0.02 ± 0.003	0.002
PNN50	1 ± 1.8	3.7 ± 3.8	0.04
RMSSD	0.009 ± 0.006	0.02 ± 0.01	0.003
Day 3			
AHR (BPM)	141.5 ± 17	132 ± 9.7	0.42
ARR (s)	0.43 ± 0.05	0.45 ± 0.03	0.47
SD_RR	0.01 ± 0.01	0.03 ± 0.009	0.16
PNN50	2.8 ± 3.7	4 ± 3.4	0.66
RMSSD	0.01 ± 0.01	0.02 ± 0.006	0.1

HRV: heart rate variability; AHR: average heart rate; BPM: beats per minute; ARR: average RR intervals; SD_RR: standard deviation of RR intervals; PNN50: percentage of consecutive RR intervals greater than 50 ms; RMSSD: root mean square of differences of standard deviation of RR intervals.

Table 5. Cumulative correlation of HRV parameters and Finnegan scores.

Parameters	Correlation coefficient	p value
AHR	r = 0.235	0.001
ARR	r = -0.238	0.0001
SD_RR	r = -0.155	0.023
PNN50	r = -0.002	0.976
RMSSD	r = -0.096	0.162

HRV: heart rate variability; AHR: average heart rate; ARR: average RR intervals; SD_RR: standard deviation of RR intervals; PNN50: percentage of consecutive RR intervals greater than 50 ms; RMSSD: root mean square of differences of standard deviation of RR intervals.

from the varied half-lives of ingested drugs during pregnancy. Jansson et al.¹⁵ modified the Finnegan score because of such concerns. In Jansson et al.'s¹⁶ evaluation of a single index of HRV in methadone withdrawal patients, neonates with lower variability on the first day of life had more NAS

Table 6. Correlation of HRV parameters and Finnegan scores by days.

Parameters	Day 1, r (p value)	Day 2, r (p value)	Day 3, r (p value)
AHR	0.27 (0.19)	0.19 (0.47)	0.13 (0.79)
ARR	-0.19 (0.35)	-0.22 (0.4)	-0.1 (0.83)
SD_RR	0.05 (0.80)	-0.07 (0.7)	-0.85 (0.03)
PNN50	0.28 (0.17)	0.04 (0.8)	-0.71 (0.11)
RMSSD	0.172 (0.42)	0.07 (0.7)	-0.9 (0.014)

HRV: heart rate variability; AHR: average heart rate; ARR: average RR intervals; SD_RR: standard deviation of RR intervals; PNN50: percentage of consecutive RR intervals greater than 50 ms; RMSSD: root mean square of differences of standard deviation of RR intervals.

symptoms on Day 3, although no controls were included. We showed a lower HRV on a daily basis in the first 48 h of life in IUDEI, and cumulatively over the first 72 h of life. Our study validated one HRV parameter that can be used on first

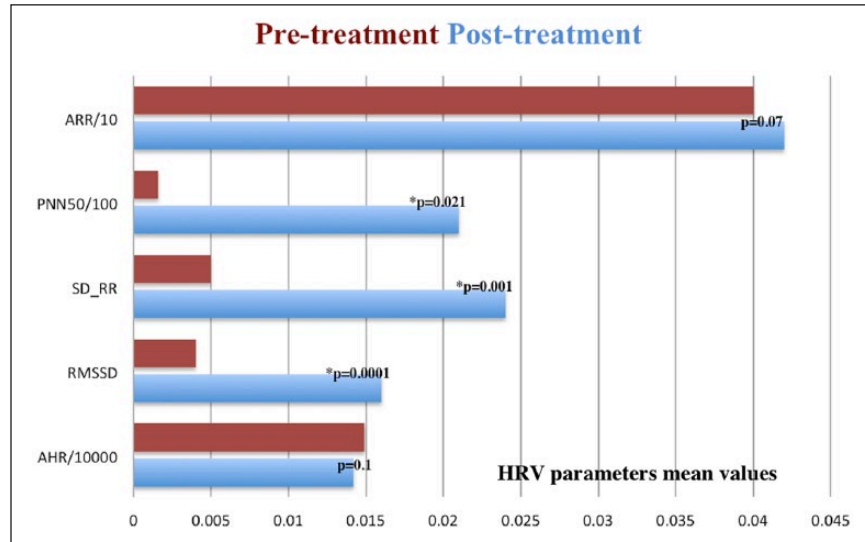


Figure 1. Effect of morphine on HRV parameters.

HRV: heart rate variability; ARR: average RR intervals; PNN50: percentage of consecutive RR intervals greater than 50 ms; SD_RR: standard deviation of RR intervals; RMSSD: root mean square of differences of standard deviation of RR intervals; AHR: average heart rate.

day of life and three parameters on Day 2 of life to differentiate IUDEI from controls. RMSSD was able to differentiate IUDEI who subsequently develop NAS and therefore require therapy.

Maternal urine drug screen covers only 72 h before delivery (except chronic marijuana) and MDS covers second and third trimester exposure. But MDS can be delayed in preterm (delayed passage of meconium up to 10 days) or inapplicable if it diffuses in-utero in perinatal hypoxia especially in post-date infants.^{17,18}

The difficulty to recruit normal neonates who met our environmental criteria for appropriate duration prompted us to use hyperbilirubinemia patients in the SCN as controls. Weissman¹¹ showed lower HRV in phototherapy-treated hyperbilirubinemia versus control group. Our study showed the lowest HRV in IUDEI compared with those with phototherapy-treated hyperbilirubinemia under the same typical environmental conditions in a SCN, which further suggests the potential higher difference in HRV parameters between normal neonates and IUDEI.

Finally, opiate-treated IUDEI showed higher HRV after treatment. Monitoring the increase in HRV can potentially reduce the subjectivity in the management of NAS. With the objectivity associated with HRV assessment compared to the Finnegan score, HRV assessment may play a role in titrating opioid therapy in IUDEI.

Study limitations

This is a pilot study to demonstrate the benefit of using HRV in IUDEI management. The sample sizes for the cases and controls are small. We hope to enroll larger sample sizes after appropriate power analysis in the near future. Another

major limitation is the potential for error in manually calculating the RR intervals. In addition, manual calculations are time consuming and are not practical in a clinical setting. We propose further studies using Holter monitors that are able to provide data immediately and efficiently while minimizing measurement error.

Another limitation is that neonates admitted for treatment of hyperbilirubinemia by phototherapy are not normal newborns. Normal neonates are admitted to labor and delivery rooms that can be quiet or loud due to visitors/TV sounds or rooms can be dim or lighted. On the contrary, SCN has visiting restrictions and only sounds available are cardiorespiratory monitor or crying baby with standard lighting conditions; this controls environmental factors for both cases and controls which are known to affect HRV parameters.¹⁴ We believe that the differences in HRV parameters will be further exaggerated when comparing normal newborns and IUDEI because it is expected that normal newborns have much higher variability than phototherapy-treated hyperbilirubinemia patients.¹¹ We think Holter monitors for infants at risk for NAS (if justified by future studies) is a potentially sustainable monitoring method because it detects higher frequency spectral analysis that reflect vagal tone and it is not affected by minute to minute changes as short term time domain. Also, HeRo monitor is now a new alternative that proved its beneficial effect in many studies.^{19,20}

Conclusion and future prospective

We used time-domain variability indices to evaluate HRV in IUDEI and phototherapy-treated hyperbilirubinemia infants. HRV can differentiate IUDEI requiring therapy from those who do not even earlier than Finnegan score. Additionally,

HRV might be useful in titration of doses of opioids during treatment of IUDEI. A possible added benefit of using HRV in IUDEI management is that Finnegan score is not validated in preterm infants,²¹ whereas HRV is validated.^{22–24} Further studies utilizing electronic monitors are needed to minimize the measurement errors associated with manual tabulation of EKGs.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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