Heart Rate Variability by Triangular Index in Infants Exposed Prenatally to Cocaine

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Background: In adults, heart rate variability triangular index (HRVi) is a highly reproducible measure of heart rate variability (HRV), which makes it more suitable for use in longitudinal studies. Although normative data have been published for newborns, studies in infants with pathological conditions are lacking.

Methods: From 1997 to 2000, within the first 4 days of life, we prospectively evaluated HRVi in cocaine-exposed asymptomatic newborns (N = 97) by Holter monitoring. Their data were compared with infants from two control groups (one with no in utero drug exposure, N = 102; the other with exposure to alcohol, nicotine, or marijuana but no cocaine, N = 111).

Results: In assessing concordance between and within operators for HRVi, the intraclass correlations were 0.983 (95% CI: 0.958, 0.994) and 0.997 (95% CI: 0.984, 0.999), respectively. Infants with in utero cocaine exposure had significantly ($P < 0.0001$) lower HRVi than those exposed to other drugs and to no drugs in utero. If abnormal HRVi is defined as < fifth percentile for the no drug exposed group ($\text{HRVi} < 8$), 10% of the cocaine-exposed newborns, in contrast to 2% in each of the control groups ($P = 0.003$) had abnormal values.

Conclusion: HRVi is a reliable measure to study heart rate variability in newborns. Asymptomatic infants with in utero cocaine exposure have lower HRVi. Our study supports the clinical use of an abnormal HRVi as a value < 8 for newborn infants.

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Heart rate variability (HRV) has been used to study newborns' (term and preterm) autonomic function^{1,2} and to assess changes in autonomic function with growth.³ It is commonly measured by a number of methods including statistical, geometric, frequency domain, and nonlinear methods. Geometric methods, particularly HRV triangular index (HRVi),^{4,5} offer an advantage for being relatively insensitive to the analytical quality of the normal beat-to-beat recording (NN intervals).⁶ HRVi is highly reproducible among different com-

mercially available analyzing systems.⁷ Furthermore, in adults, a relatively high intra-individual reproducibility makes it more suitable for use in longitudinal studies.⁸ Studies of HRVi are lacking in the pediatric population, except for recently published normative values of HRVi in normal newborn infants.⁹

Similar to adults, decreased HRV in children is a marker of "poor health" as reported in children with diabetes¹⁰ and with congenital heart disease.^{11,12} Similar to studies in neonatal rats,¹³ in-

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infants with in utero cocaine exposure during the first few days of life also have decreased HRV as measured by frequency and time domain methods.¹⁴ The purpose of this study was to determine the feasibility of using HRVi for clinical applications by assessing its reproducibility and evaluating it in a cohort of infants with in utero drug exposure including cocaine.

METHODS

Selection Criteria

As part of a study on the effects of in utero cocaine exposure on the heart, this study included 24- to 72-hour-old, asymptomatic infants from the Level-I normal newborn nursery at MetroHealth Medical Center from 1997 to 2000. These infants weighed more than 2400 g and were between 36 and 42 weeks gestation. We used a convenience sampling strategy and excluded infants from the study if they were (a) born to mothers with acute or chronic diseases; (b) symptomatic or required administration of oxygen beyond 5 min; and (c) born with associated congenital anomalies. As a part of the original study protocol, all infants had 2-D echocardiograms and Doppler examinations. Subjects with significant cardiac defects (except patent ductus arteriosus, patent foramen ovale or physiological mitral, tricuspid or pulmonary regurgitation) were excluded from the study. Infants were also excluded if they had any illicit drug exposure in utero other than alcohol, marijuana, cocaine, and nicotine.

At the time of enrollment, infant drug exposure status was determined by a structured interview questionnaire^{15,16} and by laboratory analysis of maternal and infant urine as well as meconium for cocaine and its metabolites, barbiturates, benzodiazepines, cannabinoids, opiates, phencyclidine, amphetamines, and cotinine. The frequency of drug use and the amount used per day translated into a severity score for the month prior to pregnancy and for each trimester. This score was averaged to obtain a total score for the prenatal exposure for each drug.¹⁷ The infants were considered positive for exposure to that drug based on either maternal self-report or toxicology studies. Heavy cocaine usage was defined a priori as the amount of cocaine used during the pregnancy that exceeded the 70th percentile of cocaine usage derived from our previous study.¹⁸ The remaining cocaine-ex-

posed infants were grouped under light cocaine usage. Their data were compared to two control groups not exposed to cocaine. These control groups were infants exposed to other drugs in utero (alcohol, marijuana, and/or nicotine) but not cocaine (Group 2) and infants with no in utero drug exposure (Group 3). Hospital records provided demographic and medical characteristics at the time of infant birth. The study was approved by the Institutional Review Board for human investigation at MetroHealth Medical Center at Case Western Reserve University. Informed written consent was obtained from the legal guardians/parents of all participants.

Holter Monitoring

Three-channel Holter monitors (Marquette M-8500, three-channel recorders) were used within the first 72 hours of life. Holter recordings were obtained for 24 hours. After skin preparation, electrodes were placed to record leads II, V1, and V5. A 1-mV calibration signal was recorded. A built-in clock started after electrode attachment.

A digital commercial Holter scanner (Pathfinder 700 Series, Reynolds Medical Ltd, Hertford, UK) analyzed heart rate variability from the Holter tapes. Two physicians, who were blinded to the infants' in utero drug exposure status, edited all tapes to assure accuracy of QRS classification. Average hourly heart rates were determined from the computerized Holter scanner. The system also measured the geometric triangular index (HRVi), which is the total number of all N-N intervals divided by the height of the histogram of all N-N intervals measured on a discrete scale with bins of 7.8125 ms, and with no adjustment for recording length.

Statistical Analysis

A reliability analysis was performed on the two operators who were blinded to the infants' in utero drug exposure status. Nine tapes (randomly selected) were assessed by each of the two operators and repeated assessments on eighteen randomly selected tapes were done by one of the operators.

Data were analyzed using the statistical software SAS v.8.1.¹⁹ The body surface area (BSA) was calculated based on Haycock formula.²⁰ This method has been validated in infants. Since body surface area correlated with both global heart rate variability and cocaine exposure, the difference in the

Table 1. Clinical and Demographic Data of Newborns Exposed to In Utero Cocaine Versus Exposure to Other and No Drugs

	Cocaine (N = 97)	Other Drugs (N = 111)	No Drugs (N = 102)	P Value
Gestational age (weeks)	38.48 ± 1.8	39.07 ± 1.6	39.38 ± 1.2	0.0003 ^{a,b}
Birth weight (g)	2917 ± 488	3141 ± 475	3272 ± 421	0.0001 ^{a,b}
Birth length (cm)	48.26 ± 2.7	49.64 ± 2.6	49.92 ± 2.3	0.0001 ^{a,b}
BSA (M ²)	0.20 ± 0.02	0.21 ± 0.02	0.22 ± 0.02	0.0001 ^{a,b}
Postnatal age (hours)	21.9 ± 3.1	21.2 ± 3.7	21.6 ± 3.8	> 0.1
% Male	45 (44/97)	60 (71/119)	51 (52/101)	> 0.1
% Caucasian	31 (30/97)	38 (45/119)	22 (22/101)	0.04

^a Cocaine versus no drugs; ^b Cocaine versus other drugs. BSA = body surface area.

group means for HRVi were analyzed by analysis of covariance using body surface area as the covariant. Statistical significance was defined a priori as a P value < 0.05, two-tail. If the analysis of variance/covariance was statistically significant, then post hoc comparisons with the Bonferroni correction were performed to reduce the testwise error.

RESULTS

The clinical and demographic data on the 310 infants enrolled in this study are reported in Table 1. Infants exposed to cocaine in utero had lower gestational age, birth weight, birth length, and body surface area (BSA) in comparison to the two control groups (P < 0.001).

In the cocaine-exposed infants, the heart rate was higher (P = 0.04), whereas the HRVi was lower (P < 0.0001) in comparison to those exposed to other drugs and no drugs (Table 2). Because HRVi was correlated with mean heart rate (r =

-0.58, P < 0.0001), an analysis of covariance was performed with mean heart rate and BSA as the covariates. The adjusted HRVi was still lower in the cocaine-exposed infants (P < 0.0001). The HRVi and the adjusted HRVi were lower in heavy exposed cocaine group in contrast to those with no cocaine exposure (P < 0.0001). Based on our previously reported normative newborn data,⁹ if one defines an abnormal HRVi value as being below the fifth percentile for the no drug exposed group (i.e., < 8), 10% of the cocaine-exposed infants in contrast to 2% in each of the control groups had abnormal values (P = 0.003). Based on the analysis of the severity of exposure, 12% of the infants with heavy exposure, 9% with light cocaine exposure, and 2% with no cocaine exposure had HRVi < 8 (P = 0.003).

The mean duration of analyzable data for the Holter tapes was 21.57 ± 3.58 hours (range 3-27 hours; with 92% > 12 hours). All tapes were ob-

Table 2. HRVi Data in 97 Newborn Infants Exposed to In Utero Cocaine Versus Exposure to Other and No Drugs

	Cocaine N = 97	Other Drugs N = 111	No Drugs N = 102	P Value
Heart rate	133.47 ± 9.82	130.18 ± 8.99	130.34 ± 8.17	0.04*
HRVi	12.21 ± 3.71	14.64 ± 4.25	14.12 ± 4.36	< 0.0001*
HRVi-adjusted†	12.93 ± 0.34	14.06 ± 0.32	13.63 ± 0.33	< 0.0001*

	Heavy Cocaine N = 43	Light Cocaine N = 54	No Drugs N = 213	P Value
Heart rate	134.39 ± 7.54	132.72 ± 11.35	130.26 ± 8.59	0.05*
HRVi	11.56 ± 3.67	12.72 ± 3.69	14.39 ± 4.30	< 0.0001**
HRVi-adjusted†	12.67 ± 0.52	13.12 ± 0.44	13.86 ± 0.23	< 0.0001**

Data are in means ± standard deviation except for HRVi-adjusted, which is reported as adjusted means ± standard error.

* Significant difference between cocaine versus no drugs and cocaine versus other drugs; ** significant difference between no drugs versus light cocaine and no drugs versus heavy cocaine. † Adjusted for body surface area and heart rate.

tained between the second and fourth day of life. In assessing concordance between and within operators for HRVi, the intraclass correlation coefficients were 0.983 (95% CI: 0.958, 0.994) and 0.997 (95% CI: 0.984, 0.999), respectively.

DISCUSSION

The present study is the first to report reliability and potential clinical application of HRVi in a large cohort of cocaine-exposed infants. In the immediate newborn period, infants exposed to cocaine in utero have lower HRVi than those exposed either to no drugs or to other drugs (nicotine, alcohol, or marijuana). Infants with heavier exposure to cocaine were more affected. Furthermore, our study also documents that HRVi is highly reproducible in newborn infants with excellent concordance between and within operators. As shown in other studies, it is relatively simple to measure, and among the various measures of HRV, it is least influenced by the operator and equipment.^{7,8}

To study the autonomic nervous system modulations of the heart, it may be preferable to use more than one method. Although spectral analysis has the advantage of identifying all frequency components of heart rate variability, it is more prone to errors with artifacts, arrhythmias, and noisy data. As a result, manual editing is needed to identify and label the normal R-R (N-N) intervals, making spectral analysis more operator-dependent. For example, between operators, the intraclass correlations for the frequency domain parameters ranged from 0.40 to 0.62 with high frequency being 0.62.⁹ In contrast, artifacts and ectopic beats have minimal influence on HRVi and time domain analyses. Of the latter two methods, HRVi is less influenced by computer error in automatic recognition of long-term ECG recordings than time domain indices like SDNN that measures standard deviation between normal adjacent heartbeats (N-N intervals).²¹ The intraclass correlations for the various time domain parameters are also excellent (0.73-0.88),⁹ however, HRVi offered the most consistent data in our study (0.983). Since HRVi is influenced by the number of N-N intervals, it is recommended that recordings be at least 20 minutes or more.⁶ More than 92% of our analyzable recordings were > 12 hours with minimum of 3 hours; therefore, it is recommended that a similar period of analyzable data be used in other comparable studies.

In the current study, a commercial Holter analyzer measured the geometric triangular index (HRVi) on a discrete scale with bins of 7.8125 ms, as recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.⁶ Theoretically, it may be argued that using smaller bins may have provided us with a broader range of HRVi due to higher average heart rates seen in infants. Although this may be true, most commercial software and hardware comply with the above recommendations and any alterations in the methodology may require further validation before its clinical use. Furthermore, most adult studies are in compliance with the above standards of methodology. Because the operator and commercially available analyzing systems least affect HRVi, it is ideal for use in longitudinal studies. During the long-term follow-up as the child matures into adulthood, adherence to the above guidelines are essential to preserve concordance and to facilitate interpretation during this transition period.

In adults, HRVi of < 25 is associated with electrical instability of the myocardium.⁵ In our neonatal population, the selection of HRVi of < 8 resulted in a significant separation between cocaine-exposed infants (10%) versus the two control groups (2% each). This definition of an abnormal value was based on a statistical definition (< fifth percentile of the no drug exposed group) and not on the development of a specific outcome (i.e., morbidity or mortality). It is possible that a lower value, especially in symptomatic infants, will be predictive of adverse outcomes. Nevertheless, 10% of these asymptomatic cocaine exposed infants had values below the fifth percentile of the no exposure group. In this biological model, however, several potential variables are worth considering that may influence the outcome. Besides gestational timing, duration, and dosage of cocaine exposure, other factors that can influence the action of cocaine on the developing autonomic system are dopamine transporters and receptors,²² the levels of plasma cholinesterase (primary pathway for metabolizing cocaine) activity of the mother and infant, and the placental characteristics.^{23,24} Because of our study design, only asymptomatic newborn infants were studied. It is possible that inclusion of symptomatic patients may have resulted in more pronounced effects of cocaine.

In summary, this study prospectively assessed heart rate variability by HRVi in 97 asymptomatic

cocaine-exposed newborn infants using 24-hour Holter monitoring. In the immediate neonatal period, cocaine-exposed infants had lower HRVi. HRVi, with excellent concordance between and within operators, is a reliable measure to study heart rate variability in newborn infants. Based on the values noted in normal and cocaine-exposed newborn infants, for clinical applications a HRVi value of <8 should be considered as abnormal.

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