Heart rate variability in cocaine-exposed newborn infants

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Background Infants born to cocaine-using mothers have a 3- to 8-fold increase in sudden infant death syndrome. Its underlying cause, in part, may be attributed to abnormal autonomic function. We proposed to study heart rate variability, reflecting autonomic control of the heart, in cocaine-exposed infants.

Methods From 1997 to 2000, we studied 217 asymptomatic, term infants, of whom 68 had intrauterine cocaine exposure (group I). Their data were compared with infants exposed to drugs other than cocaine (group II, n = 77) and no drugs (group III, n = 72). Twenty-four-hour heart rate variability was measured within 72 hours of birth.

Results Cocaine-exposed infants, as compared with the 2 control groups, had an overall significant decrease ($P < .05$) in global heart rate variability and a lower standard deviation of all valid N-N intervals in the recording (41.9 ± 1.4 ms vs 47.6 ± 1.3 ms and 46.9 ± 1.3 ms, respectively). Vagal parameters such as high-frequency power and the square root of the mean of the squared differences between adjacent N-N intervals were also lower in newborns with heavy in utero cocaine exposure.

Conclusions Decreased heart rate variability was seen in cocaine-exposed infants. Whether low heart rate variability is a marker for increased risk of sudden death in infants (as it is in adults with structural heart disease) is unknown and requires further investigation. (Am Heart J 2001;142:828-32.)

Heart rate variability (beat-to-beat changes in cardiac cycle length) results from modulation of sinus node function by the autonomic nervous system. Indexes of rapid modulation of cardiac cycle, including the square root of the mean of the squared differences between adjacent N-N intervals (r-MSSD) and high-frequency power (0.15 to 0.40 Hz), represent parasympathetic or vagal influence on the heart.[1,2] Both vagal and sympathetic signals affect low-frequency power (0.04 to 0.15 Hz). Global measures of heart rate variability, such as the standard deviation of all the normal heart periods over 24 hours (SDNN), reflect a complex interaction of vagal, sympathetic, humoral, and central influences. A reduction in this index has been shown to be a strong predictor of death in adults, especially after myocardial infarction.[3]

Acute intranasal administration of cocaine stimulates the central sympathetic outflow to the skin and heart.[4] Effects of repeated exposure of cocaine on the autonomic system, however, are less well understood. An increase in heart rate variability has been observed in ferrets when they are given low-dose cocaine.[5] With a higher, lethal dose of cocaine, there was a marked decrease in heart rate variability before sudden death.

In addition to effects on heart rate variability, prolonged cocaine exposure also influences the heart rate. The response of heart rate appears to be dose dependent. In utero cocaine exposure in rats had a dose-dependent effect on the heart rate. The offspring who were chronically exposed to low-dose in utero cocaine had increased heart rate, whereas a higher dose (2 times the low dose) had no effect on the heart rate.[6] In addition, both groups had a decrease in heart rate variability.

It is likely that intrauterine exposure to cocaine leads to autonomic dysfunction in neonates. Cocaine readily crosses the placenta, resulting in exposure of the developing fetal nervous and cardiovascular systems to high levels of this drug. We have observed in a preliminary study that heart rate was lower and high-frequency power was higher in infants with in utero cocaine exposure.[7] Increased heart rate variability was also observed in another study of 17 cocaine-exposed, 2-week-old infants during sleep.[8] The current prospective study was undertaken with the hypothesis that during fetal development, cocaine exposure leads to anomalous development of the autonomic control of the heart. This should be measurable as alteration of heart rate variability.

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Methods

Asymptomatic infants were eligible for the study if they were <72 hours old, weighed ≥1500 g, and were between 33 and 42 weeks of gestation. We used a convenience sampling strategy with the goal of enrolling 2 control infants for each cocaine-exposed infant. Since cocaine-exposed infants (group I) were likely to be exposed to other drugs in utero, especially alcohol, marijuana (THC), and/or nicotine, the first control group was infants with exposure to alcohol, THC, and/or nicotine (group II). The second control group had no intrauterine drug exposure (group III). The exclusion criteria were maternal use of any medications during the pregnancy that may affect the cardiovascular system (such as bronchodilators); any acute (such as preeclampsia) or chronic maternal diseases (such as hypertension, hepatitis, diabetes, and HIV infection); any neonatal illnesses (such as hypoglycemia, sepsis, use of supplemental oxygen beyond 5 minutes of life), ventilatory support, admission to neonatal intensive care unit, or any congenital anomalies except patent ductus arteriosus, patent foramen ovale, or physiologic mitral, tricuspid, or pulmonary regurgitation.

Drug exposure

At the time of enrollment, maternal urine as well as infant urine and meconium underwent testing for cocaine and its metabolites, barbiturates, benzodiazepines, cannabanoids, opiates, phencycladine, amphetamines, and cotinine. The samples were first screened by the Enzyme Multiplied Immunoassay Technique. If the urine sample was positive, the result was then confirmed by thin-layer chromatography with the Toxi-lab system (Ansys Diagnostics Inc, Irving, Calif). If the meconium sample was positive, the result was confirmed by gas chromatography followed by mass spectrometry. The cocaine metabolites measured in the samples were cocaine, benzoylecgonine, and m-OH-benzoylecgonine, with the addition of coca-ethylene in the meconium. Infants and their biological mothers were seen as soon as possible after birth, at which time the care giver was interviewed regarding drug abuse. An adaptation of the Maternal Post-Partum Questionnaire[9,10] was used to quantify maternal drug use. For the month before pregnancy and for each trimester of pregnancy, mothers were requested to recall frequency and amount of drug use. For tobacco, the number of cigarettes smoked per day was recorded. For marijuana, the number of joints per day, and for alcohol, the number of drinks of beer, wine, or hard liquor was computed with each drink equivalent to 0.5 ounces of absolute alcohol. For each drug, the frequency of use was recorded on a Likert-type scale ranging from 0 (not at all) to 7 (daily use), which was then converted to reflect the average number of days per week a drug was used. The frequency of use was multiplied by the amount used per day to compute a severity of use score for the month before pregnancy and for each trimester. This score was then averaged for a total score for the prenatal exposure for each drug.[11] The patient was considered positive for use of that drug by either 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.[12]

Demographic and medical characteristics at the time of infant birth were abstracted from the hospital record. These included maternal race, age, gravidity, parity, number of prenatal care visits, type of medical insurance, infant Apgar scores, birth weight, length, head circumference, estimated gestational age, and infant small-for-gestational-age status. 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 or parents of all participants.

Holter monitoring

Three-channel Holter monitors (Marquette M-8500, 3-channel recorders) were placed within the first 48 hours of life. Holter recordings were obtained for 24 hours. After skin preparation, electrodes were placed to record leads II, V_1, and V_5. A 1-mV calibration signal was recorded for 5 minutes, and control recordings were obtained in different postures to evaluate ST-segment shift with position. A built-in clock started after electrode attachment.

A digital commercial Holter scanner (Pathfinder 700 Series, Reynolds Medical Ltd, Hertford, UK) was used to analyze the arrhythmias, spectral analysis, and ST changes from the Holter tapes. All tapes were edited to ensure accuracy of QRS classification. Ectopic beats were manually identified and then excluded from the analysis of heart rate variability. The individuals who edited and read the tapes were blinded to the infant's history of prenatal drug exposure. Average hourly heart rates were determined from computerized Holter scanner. Maximum, minimum, and mean 24-hour heart rates with standard deviations were calculated for each subject. In addition, arrhythmias were identified and defined as ectopic beats (premature atrial contractions or premature ventricular contractions) per hour.

The following time-domain parameters were computed: (1) mean heart rate, (2) RMSSD, the square root of the mean of the squared differences between adjacent N-N intervals over the 24-hour recording; and (3) SDNN, standard deviation of all valid N-N intervals in the recording. The following frequency-domain parameters were obtained (power is expressed as ms^2): (1) high- frequency power, frequency range of 0.15 to 0.40 Hz; (2) low-frequency power, frequency range of 0.04 to 0.15 Hz; and (3) total frequency power (total), frequencies <0.4 Hz.

Data were analyzed with the use of SAS V8.0 (SAS Inc, Chapel Hill, NC). The Holter monitor data were transformed by the square root transformation when appropriate to achieve normality. The data were transformed back and presented as means and standard deviations in the tables. The body surface area (BSA) was calculated on the basis of the Haycock formula.[13] This method has been validated in infants. Because BSA correlated with both global heart rate variability and cocaine exposure, differences in group means for all Holter data were analyzed by analysis of covariance with BSA used as the covariant. Post hoc comparisons were adjusted by Bonferroni corrections.

Results

Two hundred seventeen asymptomatic infants who were <72 hours old were enrolled in this study. Mothers of 68 cocaine-exposed infants (group I) also used

Table I. Demographics data

	Cocaine group I (n = 68)	Other drugs group II (n = 77)	No drugs group III (n = 72)	*P* value
Infants				
Sex (percent boys)	48 (33/68)	61 (47/77)	51 (38/72)	.36
Birth weight (g)	2890 ± 509	3177 ± 491	3258 ± 419	.0001*†
Birth length (cm)	48.1 ± 2.92	49.9 ± 2.70	49.8 ± 2.37	.0001*†
Head circumference (cm)	33.2 ± 1.55	33.9 ± 1.67	34.1 ± 1.35	.001*†
Gestational age (wk)	38.6 ± 1.73	39.2 ± 1.44	39.4 ± 1.23	.006*†
BSA (m^2)	0.20 ± 0.02	0.21 ± 0.02	0.21 ± 0.02	.0001*†
Mothers				
Age (y)	29.7 ± 5.61	23.4 ± 4.77	21.5 ± 3.26	.0001*†‡
Race (% white)	31 (21/68)	38 (29/77)	22 (16/72)	.11
Percent employed	10 (7/67)	22 (17/76)	33 (23/69)	.006*†
Education (y)	10.9 ± 1.74	11.1 ± 1.77	11.7 ± 1.67	.02*
Drug use				
Cigarettes (dose/d)	9.8 ± 8.75	5.6 ± 6.82	0	
Alcohol (dose/wk)	4.3 ± 7.77	0.88 ± 2.68	0	
Marijuana (dose/wk)	0.71 ± 2.24	0.74 ± 1.98	0	
Cocaine (dose/wk)	17.16 ± 42.54	0	0	

*Cocaine group I vs no drugs group III.
†Cocaine group I vs other drugs group II.
‡Other drugs group II vs no drugs group III.

Table II. Adjusted heart rate variability in three predefined groups

	Cocaine group I (n = 68)	Other drugs group II (n = 77)	No drugs group III (n = 72)	*P* value
Mean HR (beats/min)	133.6 ± 10.09	129.6 ± 9.06	130.2 ± 8.02	.08
RMSSD (ms)	20.4 ± 6.84	22.4 ± 7.08	21.5 ± 6.75	.23
SDNN (ms)	41.3 ± 10.45	48.1 ± 11.81	46.9 ± 11.35	.007*†
HF (ms^2)	48.8 ± 43.67	72.3 ± 62.09	58.6 ± 44.03	.01†
LF (ms^2)	118.6 ± 90.69	166.3 ± 108.34	139.4 ± 80.00	.009†
Total (ms^2)	851.9 ± 556.60	1193.5 ± 672.65	1064.9 ± 559.01	.01†

HF, High-frequency power (range, 0.15 to 0.40 Hz); *LF,* low- frequency power (range, 0.04 to 0.15 Hz); *RMSSD,* square root of the mean of squared differences between adjacent N-N intervals over 24-hour recording; *SDNN,* standard deviation of all valid N-N intervals in recording; *Total,* total frequency power (<0.4 Hz).
*Cocaine group I vs no drugs group III ($P < .05$, Bonferroni correction).
†Cocaine group I vs other drugs group II ($P < .05$, Bonferroni correction).

alcohol (71%), marijuana (32%), and nicotine (93%), whereas mothers in the first control group (group II, n = 77) used alcohol (49%), marijuana (27%), and nicotine (71%) but no cocaine. The second control group (group III, no drugs, n = 72) of infants was free of all drugs. On the basis of the mother's use of cocaine in group I, cocaine-positive infants were further grouped into heavy exposure (n = 37) and light exposure (n = 31).[12]

The patient characteristics for these 3 groups are reported in Table I. Five-minute Apgar scores were similar among all 3 groups (reported as medians, 25th to 75th percentile scores: 9, 9 to 9; 9, 9 to 9; and 9, 9 to 9, respectively). As noted in other studies, cocaine-exposed infants had lower gestational age, birth weight, length, and head circumference.[14] Mothers who used cocaine were older, had less education, fewer prenatal visits, more pregnancies, and pregnancy losses than the other 2 groups. Among all 3 groups, Apgar score at 5 minutes and socioeconomic status were similar.

Body surface area and gestational age were significantly correlated ($r = 0.58$, $P < .001$). Similar results were obtained when heart rate variability data were adjusted for either parameter or were nonadjusted. In all models, heart rate variability was lower in cocaine-exposed neonates (Table II), especially in those with heavy cocaine exposure (Table III).

Eight neonates (group I, n = 3; group II, n = 4; group III, n = 1) had frequent premature atrial and ventricular ectopic beats. Two subjects, one each from the cocaine-exposed group and the no-drug–exposed group, had accelerated junctional rhythm. Five other neonates (group I, n = 2; group II, n = 1; group III, n = 2) had rare premature atrial and ventricular complexes.

Table III. Heart rate variability according to degree of cocaine exposure

	Heavy cocaine (n = 37)	Light cocaine (n = 31)	No cocaine (n = 149)	*P* value
Mean HR (beats/min)	134.9 ± 7.54	132.1 ± 12.44	129.9 ± 8.55	.04*
RMSSD (ms)	18.9 ± 6.25	22.2 ± 7.18	22.0 ± 6.91	.04*
SDNN (ms)	39.1 ± 9.29	43.9 ± 11.27	47.5 ± 11.57	.003*
HF (ms^2)	42.6 ± 31.36	56.5 ± 54.87	65.8 ± 54.44	.02*
LF (ms^2)	108.5 ± 90.71	131.0 ± 90.64	153.4 ± 96.42	.02*
Total (ms^2)	752.4 ± 519.51	971.3 ± 584.49	1131.8 ± 621.99	.007*

HR, Mean heart rate; *HF,* high-frequency power (range, 0.15 to 0.40 Hz); *LF,* low-frequency power (range, 0.04 to 0.15 Hz); *RMSSD,* square root of the mean of squared differences between adjacent N-N intervals over 24-hour recording; *SDNN,* standard deviation of all valid N-N intervals in recording; *Total,* total frequency power (<0.4 Hz).
*Heavy cocaine vs no cocaine ($P < .05$, Bonferroni correction).

Discussion

In our study, infants with intrauterine cocaine exposure had a decrease in both vagal and global heart rate variability indexes. These differences were more pronounced in newborns with heavy cocaine exposure than in infants with either light cocaine exposure or no cocaine exposure.

In contrast to our initial report based on only 21 cocaine-exposed infants,[7] the current study includes an enhanced sample size, an extensive drug interview, and toxicologic studies, especially for metabolites, and an additional control group of mothers using other illicit drugs (group II). In our previous study, cocaine-abusing mothers were excluded if they used any other drugs; therefore, it is likely that those mothers were light or occasional cocaine users, whereas the current cocaine group is more representative of the cocaine-abusing population. A higher heart rate variability during sleep in 2-week old cocaine-exposed infants (n = 17)[8] may be the result of altered cardiorespiratory influence of sleep on heart rate variability or it may be a reflection of nonacute effects of cocaine on the autonomic system.

In adults after myocardial infarction, a decrease in heart rate variability is associated with a higher death rate.[3] Long-term effects of decreased variability in infants is unknown. Some investigators have demonstrated a 3- to 8-fold increase in sudden infant death in cocaine-exposed infants in contrast to those who were not exposed to cocaine (4.62 in 1000 vs 1.39 in 1000,[15] 8.36 in 1000 vs 1.22 in 1000,[16] 9.3 in 1000 vs 1.3/1000[17]).The cause of sudden death in cocaine-exposed infants remains unclear. An earlier study reported 18 prenatally cocaine-exposed infants having sustained arrhythmias leading to congestive heart failure, cardiorespiratory arrest, and death.[18] It may be hypothesized that cocaine-exposed infants with decreased heart rate variability are at a greater risk for sudden death or future cardiovascular morbidity. The value of heart rate variability as a predictor of cardiac morbidity and mortality has not been evaluated.

Decreased heart rate variability indicates a disturbance of autonomic function or decreased ability of the sinus node to respond to extrinsic signals. Decreased heart rate variability is seen in many conditions (diabetes with poor metabolic control,[19] congestive heart failure,[20] and major depression)[21] and may be a marker of "poor health." Low heart rate variability is associated with congenital heart disease before surgery. It further decreases during the postoperative period and after prolonged hospitalization.[22] The reduction in heart rate variability correlated better with functional limitation than with hemodynamic disturbances of congenital cardiac lesions.[23] Hemodynamic disturbances after certain surgical procedures, particularly in the right atrium, however, may influence the autonomic nervous system. Heart rate variability indexes (RMSSD, high-frequency power, low-frequency power, and total power) were lower among 39 patients with total cavopulmonary and atriopulmonary connections.[24] On the contrary, "healthy" habits such as physical training increased the heart rate variability, primarily through increased vagal tone, among 17 obese children.[25]

In our study, there were significant demographic differences among the 3 groups: the group exposed to cocaine, the group exposed to other drugs, and the control group. Several of these differences are characteristic of cocaine-abusing mothers, as reported by Singer et al.[26] None of the demographic differences were significantly related to our parameters of spectral analysis except for the BSA.

Although heart rate variability is a noninvasive and relatively easy to perform, it should be emphasized that noisy data, artifacts, and ectopic beats, unless carefully screened, may distort the measurements. Despite advanced software programming and multiple algorithms, a careful manual editing remains mandatory to label the normal beats versus other artifacts or ectopic beats. Whereas arrhythmia is frequent in adults, particularly in adults with heart disease, most of our subjects had no significant arrhythmia. In contrast, we often encountered noisy data (during crying periods) that had to be carefully excluded. Although frequency-domain

analysis can aid in identifying parasympathetic and sympathetic activity, time-domain analysis is least influenced by ectopic complexes and artifact. Therefore we elected to analyze both sets of parameters for our study. We did not analyze our data separately during sleep and awake periods for practical reasons. Our neonatal subjects were asleep for significant amounts of time. Crying during wakeful periods introduced noise in many recordings.

Our study has demonstrated that cocaine alters heart rate variability in newborns during the first 3 days of life, consistent with autonomic disturbance. Our study does not address the question of whether these alterations are transient (ie, related to the acute effects of cocaine) or if they are long-term effects implying alterations to the developing autonomic nervous system. Our study also does not support (or refute) any long-term prognostic implications of lower heart rate variability in cocaine-exposed infants. Accordingly, long-range follow-up of cocaine-exposed infants is essential to answer these questions. Furthermore, more research will still be needed to determine the prognostic value and clinical utility of the various heart rate variability parameters in these infants.

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