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Autonomic alterations in cocaine-exposed infants

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Abstract

Background—Heart rate variability (HRV) reflects autonomic control of the heart. After intrauterine cocaine exposure, asymptomatic newborn infants within 72 hours of life have decreased HRV. It is unknown whether these alterations are transient (acute effect) or persist in older infants and possibly reflect a teratogenic effect of cocaine.

Methods—This study prospectively evaluated HRV in 2– to 6–month-old infants who were exposed to cocaine in-utero (Group 1, n = 71). Their data were compared to normal controls (Group 3, n = 77) and to newborns exposed to drugs other than cocaine (Group 2, n = 89). Based on our previous study, heavy and light cocaine exposure was also defined a priori as the amount of cocaine used during the pregnancy that was more than or less than the 70th percentile, respectively.

Results—At the age of 2 to 6 months, infants with in-utero cocaine exposure had higher vagal tone and higher HRV (total power) than normal controls (no exposure to drugs). Most of this increase in vagal tone occurred in the light–cocaine-exposure group. HRV and vagal tone in the heavy–cocaine-exposure group were similar to the noncocaine-exposed group.

Conclusions—At 2 to 6 months of age, asymptomatic infants exposed to cocaine in-utero have recovered from lower HRV seen within 72 hours of age. Infants exposed to light cocaine recovered by a rebound by increasing their vagal tone to above-normal levels. A similar response was blunted in heavily–cocaine-exposed infants. These alterations noted at follow up suggest a possible teratogenic effect of cocaine on the developing autonomic system. (Am Heart J 2002;144: 1109–15.)

Prenatally–cocaine-exposed infants may have structural cardiovascular malformations, cardiopulmonary autonomic dysfunction, and sustained arrhythmias leading to congestive heart failure, cardiorespiratory arrest, and death.[1,2] Cocaine also influences the cardiovascular and autonomic systems through its actions on baroreflex mechanisms[3] and the sympathetic nervous activity.

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Heart rate variability (HRV) is a noninvasive method to evaluate the autonomic function. HRV (beat-to-beat changes in cardiac cycle length) results from modulation of the sinus node; the degree of variability reflects a complex interaction of vagal, sympathetic, humoral, and central nervous system influences. Indices of rapid modulation of the cardiac cycle such as RMSSD (average of the hourly square root of the mean of the sum of the squares of differences between adjacent N-N intervals), SNN-50 (sum of all pairs of adjacent N-N intervals differing by >50 ms, standardized for the total of invalid intervals and the length of the recording), and HF (high-frequency power; frequency range of 0.15–0.4 Hz) represent parasympathetic or vagal influence on the heart.[4] Decreased HRV is an important predictor of adverse outcomes in a variety of conditions ranging from development of neuropathy in individuals with diabetes to mortality after myocardial infarction in adults.[5,6] A lower HRV and a lower vagal tone were noted within the first 72 hours of life in cocaine-exposed infants.[7] These infants with a lower HRV and vagal tone were asymptomatic (and in clinical practice considered “normal”) and were discharged from normal newborn nurseries.

The long-term effects of cocaine on the newborns’ autonomic function and the natural history of the above cardiac alterations seen in cocaine-exposed newborn infants, however, have received little attention. This study reports the follow-up of cocaine-exposed infants at the age of 2 to 6 months, who were asymptomatic during the first 72 hours of life, but initially had lower HRV.[7]

Methods

Between 1997 and 2000, asymptomatic infants who were <72 hours old, weighed >1500 grams, and were between 33 and 42 weeks gestation were prospectively enrolled in the study. Infants were excluded if they or their mothers had significant medical or surgical problems or if they had any illicit drug exposure in-utero other than alcohol, marijuana, cocaine, and nicotine.[7] Group 1 included cocaine-exposed infants; many of them were also exposed to other drugs inutero such as alcohol, marijuana (THC) and/or nicotine. Of the 2 control groups, the first comprised infants with exposure to alcohol, THC and/or nicotine (Group 2), and a second control group had no intrauterine drug exposure (Group 3). At the time of enrollment, infant drug exposure was determined by a structured interview questionnaire[8,9] and by laboratory analysis of maternal and infant urine as well as meconium testing for cocaine and its metabolites, barbiturates, benzodiazepines, cannabanoids, opiates, phencycladine, amphetamines, and cotinine. The frequency of drug 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 to obtain a total score for the prenatal exposure for each drug.[10] The infant was considered positive for exposure to that drug on the basis of 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. This was derived from our previous study.[11] The remaining cocaine-exposed infants were defined as light cocaine. Their data were compared with infants not exposed to cocaine (Group 2 and Group 3). Demographic and medical characteristics at the time of infant birth were abstracted from the hospital records.

The above infants were studied again at the age of 2 to 6 months at the General Clinical Research Center of MetroHealth Medical Center. After the initial history (Maternal Post-Partum Questionnaire) and physical examination, these infants underwent Holter monitor examinations. 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.

Three-channel Holter monitor (Marquette M-8500, 3 channel recorders, GE Medical Systems Information Technologies Inc, Milwaukee, Wis) recordings were obtained for 24 hours. A digital commercial Holter scanner (Pathfinder 700 Series, Reynolds Medical Ltd, Hertford, United Kingdom) was used to analyze rhythm and HRV (time and frequency domain indices) from the Holter tapes. Except for the 2 individuals involved in the drug interviews and pediatric care (LGF and DMS), all clinical investigators, including individuals analyzing the tapes, were blinded to the drug exposure status of the subjects. All tapes were edited to assure accuracy of QRS classification. Ectopic beats, noisy data and artifacts were manually identified and then excluded from the analysis of HRV. Average hourly heart rates were determined from the computerized Holter scanner. Maximum, minimum, and mean 24-hour heart rates with standard deviations were calculated for each subject. Blood pressures were recorded at birth and at the age of 2 to 6 months with the help of a Dinamap (Johnson & Johnson Medical Inc, Tampa, Fla). An average of the 2 sets of blood pressure readings for each visit was used for the analysis.

From the analysis of the Holter tapes, the following 6 time-domain parameters were acquired: mean N-N interval (average of all notmal-to-normal beats [reflects heart rate (HR)]), SNN-50, SDNN (standard deviation of all valid N-N intervals in the recording [reflects total HRV]), SDANN (standard deviation of the average of valid N-N intervals in 5-minute segments in the recording [this measure is similar to ultralow frequency of the frequency domain method]), SDNNi (average of the hourly means of the standard deviations of all N-N intervals in 5-minute segments in the recording), and RMSSD. Additionally, the following frequency domain parameters were obtained (power is expressed as ms^2): HF, LF (low-frequency power; frequency range of 0.04–0.15 Hz [reflects vagal and sympathetic tone]), VLF (very-low frequency power; frequency range of 0.0033–0.04 Hz [physiological correlates are unknown]), ULF (ultralow-frequency power; frequency range of <0.0033 Hz [this measure is similar to SDANN of the time-domain method (physiologic correlates unknown)]), and total power (frequencies ≤0.4 Hz [reflects total HRV]). The VLF and ULF represent 95% of total power.[5]

Data were analyzed with the statistical software SAS version 8.1 (SAS Institute Inc, Cary, NC). A reliability analysis was performed on the 2 operators that participated in the study. Fourteen randomly selected tapes were analyzed once by each of the operators. The intra-class correlations for the time-domain parameters ranged from 0.73 to 0.88, whereas for the frequency domain parameters ranged from 0.40 to 0.62, with high frequency being 0.62. Repeated assessments on 8 randomly selected tapes were done by one of the operators. The intra-class correlations were all excellent (range 0.90–0.99) with 11 out of 16 being ≥0.98.

Hypothesis testing regarding group differences for demographics was performed by use of analysis of variance. Distributional assumptions were assessed to test for appropriate underlying assumptions. Statistical significance was defined a priori as a *P* value <.05, 2-tail. Repeated measures of Holter monitor variables, within 72 hours of birth and at 2 to 6 month follow-up, were analyzed and compared between the 3 groups by use of the method of maximum likelihood, assuming a repeated measures analysis for unbalanced data (SAS PROS MIXED). For each analysis it was assumed that a model with separate means at each time point for each group fits the data. This is a reasonable assumption for repeated measures data with 2 time points. Also, the group mean at each time point is of interest. The covariance structure of the repeated measures is modeled by use of an unstructured model. This makes no assumption about the correlation structure of the repeated measures and allows different variance estimates at each time point. Under the means model, overall tests are obtained (as in an analysis of variance) for group, age, and group × age interaction. A significant group × age interaction indicated that the profiles of the mean responses over time are not parallel for the 3 groups, indicating an effect of group that differs over time. Another way to interpret this interaction is that the change (delta) between the 2 time points differs between the groups. In addition to estimating the mean responses by group across time, we also tested specific hypotheses about the difference between groups, under the means model. Two specific a priori hypotheses that were tested are the following: hypothesis 1, the means of the groups are not different at birth; hypothesis 2, the means of the groups are not different at the 2-month follow-up assessment. If the means were statistically different, post hoc testing was then performed with the Bonferroni correction to reduce test-wise error.

For each outcome variable, observed mean and standard deviation are reported. The square-root transformation was used for all Holter monitor outcomes to achieve normality because this type of repeated-measures analysis required each outcome to be multivariate normal. All models controlled for body surface area as measured by the Haycock Formula.[12]

Results

Of the initially enrolled newborns (n = 302), 237 (78%) were restudied; 95% of the studied infants were between the ages of 2 and 6 months. There were 71 (71 infants from the initial 95 newborns, 75%) cocaine-exposed infants (Group 1); 89 (89 infants from the initial 110 newborns, 81%) were exposed to other drugs but not cocaine (Group 2); and 77 (77 infants from the initial 97 newborns, 79%) were not exposed to any drugs (Group 3). The infant characteristics at birth and at follow-up for these 3 groups are reported in Table I. Among all 3 groups at the follow-up assessment, postnatal age and body surface area were similar. No significant difference was noted among Group 1, 2, and 3 for systolic (73.8 ± 11, 73.6 ± 11, 73.8 ± 10 mm Hg, respectively, $P = .99$) and diastolic (43.9 ± 8, 45.2 ± 8, 45.3 ± 8 mm Hg, respectively, $P = .47$) blood pressures at birth or systolic (96.9 ± 13, 98.3 ± 12, 98.4 ± 12 mm Hg, respectively, $P = .73$) and diastolic (53.3 ± 15, 55.2 ± 12, 53.9 ± 13 mm Hg, respectively, $P = .71$) blood pressures at the age of 2 to 6 months. Blood pressures were also similar among infants with prenatal exposure to heavy cocaine, light cocaine, and no cocaine (at birth, systolic 73.3 ± 11, 74.3 ± 11, 73.7 ± 11 mm Hg, $P = .91$, diastolic 43.2 ± 7, 44.6 ± 8, 45.2 ± 8 mm Hg, $P = .34$, respectively; at 2 to 6 months of age, systolic 94.5 ± 12, 99.2

± 14, 98.4 ± 12 mm Hg, $P = .21$, diastolic 50.1 ± 12, 56.4 ± 17, 54.6 ± 13 mm Hg, $P = .12$, respectively).

Cocaine-exposed newborn infants at birth, compared with the 2 control groups, had a decrease in global HRV—a lower SDNN and a decrease in vagal tone (HF, SNN-50 and RMSSD) (Tables II and III). These variables were adjusted for body surface area. At 2 to 6 months of age, however, the cocaine-exposed group had significantly higher vagal tone (SNN-50 and RMSSD) and higher HRV (total power) than normal controls (no drugs). Further evaluation of this group revealed that most of this increase in vagal tone occurred in the light–cocaine-exposure group (HF, SNN-50 and RMSSD). Although the increase in HRV and vagal tone from birth to 2 to 6 months (delta) was significant in the heavy–cocaine-exposure group (total power $P = .007$, HF $P = .001$, and SNN-50 $P = .003$), the end-results were similar to the non–cocaine-exposed group.

Discussion

Our previous study and this study of autonomic control of the heart document that neonates exposed to cocaine before birth have lower vagal tone and a decrease in HRV. At the age of 2 to 6 months, infants exposed to light cocaine use in-utero recovered with a rebound in their vagal tone to a level above the normal control group. A similar phenomenon of overshoot was not apparent in heavily–cocaine-exposed infants. Their autonomic control was similar to normal controls at 2 to 6 months of age. These findings have not been previously reported.

A study of repeated cocaine exposure on the autonomic system in adults demonstrated a decrease in vagal tone, vagal index, and heart period complexity.[13] Similarly, at birth, we observed a decrease in HRV. In another study of 2-week-old cocaine-exposed infants during sleep (n = 17), however, the HRV was increased[14]; in 11 of the 17 subjects it was thought to be due to higher sympathetic control.[15] In the present study, infants with lighter in-utero cocaine exposure developed higher than normal vagal tone at the age of 2 to 6 months. Infants with heavy in-utero cocaine exposure did not show this overshoot phenomenon; instead they normalized at 2 to 6 months from the initially depressed HRV. It is unclear why the light–cocaine-exposure infants developed higher vagal tone, but it could be speculated that chronic light cocaine exposure produced a delayed “training effect” such as is seen in athletes, or that these infants somehow overcompensated for their earlier effect on HRV. Although light–cocaine-exposed newborns initially had lower HRV (as evident by lower HF, LF, VLF, ULF, and total power) than non–cocaine-exposed infants, these values did not reach statistical significance. In the heavy–cocaine-exposed infants, deleterious effects of cocaine exposure may have interfered with such compensatory mechanisms.

The fact that cardiac effects of in-utero exposure of cocaine in apparently healthy infants continue until the age of 2 to 6 months suggests a teratogenic effect (reversible or irreversible). By crossing the utero-placental barrier,[16] cocaine has the potential of altering fetal brain development that may lead to long-term, if not permanent, nervous system alterations.[17] Cocaine use by pregnant women affects newborns’ central nervous system maturation and leads to altered neonatal behavior.[18] In 1-year-old children, a positive linear relationship was noted between cocaine’s teratogenic effects on auditory comprehension and

the amount of prenatal cocaine exposure.[19] Vagal activity of infants, as assessed by HRV, also plays a major role in information processing and is predictive of future behavior.[20,21]

The teratogenic effect of cocaine may be related to its ability to limit the action of serotonin on sensory pathways; serotonin plays a major role in the development of sensory pathways in various organs, including the heart and brain.[22] Between 3 to 6 years of age, vagal tone increases significantly in normal children.[23,24] A thought-provoking question remains whether heavily–cocaine-exposed infants will increase their vagal tone with age. This was observed in rat models where cocaine attenuated the age-dependent change in HRV.[25]

Similar to adults, diabetic children with poor metabolic control have lower HRV.[26] Although the studies of HRV in children are limited, low HRV in children is considered a marker of “poor health.” Preoperative low HRV in children with congenital heart disease lowers further during the postoperative period and after prolonged hospitalization.[27] A reduction in HRV was also seen with functional limitations and hemodynamic disturbances associated with congenital cardiac lesions and after cardiac surgery.[28,29] Severely diminished parasympathetic nerve activity with a normal or accelerated sympathetic nerve activity after Fontan repair has been postulated to be arrhythmogenic.[30] On the contrary, “healthy” habits like physical training increase heart rate variability.[31]

In our study, there were no significant differences in the blood pressures at birth and at 2 to 6 months of age among the 3 groups. In addition, the degree of cocaine exposure also had no significant effect on their blood pressures. Long-term follow up of HRV and blood pressures of this cohort is crucial because autonomic function after puberty plays an important role in increasing blood pressure levels associated with increased modulation of vagal tone of the heart.[32]

Despite advanced software programming and multiple algorithms, the measurement of frequency domain parameters still requires careful manual editing to exclude noisy data, artifacts, and ectopic beats. In our subjects, noisy data had to be screened carefully. Our intra-class correlations showed high reproducibility for time domain measures with lower values for frequency domain measures, which are more operator dependent. We elected to analyze both sets of parameters for our study because the frequency domain parameters provide a full spectrum of the HRV parameters, and time domain analysis is least influenced by ectopic complexes and artifacts and hence is relatively operator independent. We did not analyze our data separately during sleep and wake periods because the transition periods were less defined. Additionally, our neonatal subjects were asleep for significant amounts of time. The extent of genetic contribution and the possible influence of particle and ozone exposure on the HRV, which has been reported in adults, could not be evaluated in the present study.[33,34] It should also be noted that various components of HRV reflect the degree of autonomic modulations and not the level of autonomic tone. Furthermore, the relationship between HRV and parasympathetic effect is non linear.[35]

In summary, in this large prospective cohort study, at birth and 2 to 6 months of age, cocaine-exposed infants who are asymptomatic and appear “normal” have altered autonomic function. Infants exposed to lighter cocaine use in-utero recovered with an exaggerated

increase in their vagal tone. An exaggerated recovery was not seen in heavily–cocaine-exposed infants. This suggests a possible teratogenic effect of cocaine on the developing autonomic system. Long-term implications of the above cardiac and autonomic alterations secondary to in-utero cocaine exposure remain unknown. Ongoing studies are pivotal to answer the long-term significance of these findings.

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Table I.

Demographics of infants at birth and follow up

	Group 1 (cocaine)	Group 2 (other drugs)	Group 3 (controls)	*P*
At birth				
Sample size (n)	95	110	97	
Male (%)	46	60	50	.11
Gestational age (weeks)	38.4 ± 1.9	39.0 ± 1.6	39.4 ± 1.2	.0001 *,†
Weight (kg)	2.9 ± 5.0	3.1 ± 4.9	3.2 ± 4.2	.0001 *,†
Length (cm)	48.2 ± 2.8	49.6 ± 2.6	49.8 ± 2.2	.0001 *,†
Head circumference (cm)	33.3 ± 1.5	33.9 ± 1.6	34.2 ± 1.4	.0001 *,†
White (%)	31	38	21	.02‡
At follow up				
Sample size (n)	71	89	77	
Age (months)	2.8 ± 2.1	2.3 ± 1.0	2.5 ± 2.6	.19
Body surface area (m^2)	0.20 ± 0.03	0.21 ± 0.03	0.21 ± 0.03	.26

*Cocaine versus controls at birth.

†Cocaine versus other drugs at birth.

‡Other drugs versus no drugs at birth.

Table II.

HRV data among the 3 groups (observed means and standard errors)

	Group 1 (Cocaine)	Group 2 (Other drugs)	Group 3 (No drugs)	*P*
Sample size (n)				
Birth	95	110	97	
2–6 months	71	89	77	
HR				
Birth	132.75(0.93)	130.27 (0.85)	130.67 (0.92)	.127
2–6 months	142.74(1.08)¶	141.88 (0.95)¶	143.70(1.04)¶	.431
RMSSD				
Birth	20.33 (0.63)	22.04 (0.65)	21.19 (0.59)	.088
2–6 months	21.97 (0.80)¶	20.39 (0.45)	19.65 (0.56)	.022§
SDNN				
Birth	41.88(1.15)	47.64(1.15)	46.82(1.23)	.002†‡
2–6 months	49.94(1.14)¶	49.07 (1.00)	47.82(1.04)	.297
HF				
Birth	50.32 (3.89)	69.36 (5.54)	59.04 (4.37)	.006‡
2–6 months	75.54 (7.49)¶	62.15 (4.49)	60.63 (5.07)	.089
LF				
Birth	122.99 (8.89)	161.23 (10.69)	138.61 (8.13)	.012‡
2–6 months	150.34(11.94)¶	145.34 (9.74)	134.09 (7.97)	.271
Total				
Birth	872.97 (59.76)	1196.00 (83.01)	1125.44 (79.70)	.234
2–6 months	1224.38 (93.91)¶	1215.15(127.79)	1097.37(92.84)	.021 §
VLF				
Birth	251.40 (26.15)	303.65 (23.55)	271.36 (21.07)	.858
2–6 months	208.98 (20.61)	276.45 (60.54)	211.15 (32.30)¶	.263
ULF				
Birth	472.46(32.81)	661.47 (57.85)	656.79 (59.75)	.176

	Group 1 (Cocaine)	Group 2 (Other drugs)	Group 3 (No drugs)	*P*
2–6 months	792.69 (65.08)[¶]	732.27 (65.24)	691.77 (59.87)	.013[§,//]
SNN-50				
Birth	4320.09 (404.41)	5743.43 (468.23)	4835.27 (425.12)	.047[‡]
2–6 months	6565.65 (709.79)[¶]	4905.06 (406.52)	4752.39 (519.28)	.025[§]
SDNNI				
Birth	27.78 (0.90)	31.33 (0.91)	30.46 (0.95)	.035[‡]
2–6 months	29.61 (0.86)	29.18(0.71)	28.23 (0.66)	.288
SDANN				
Birth	31.89(1.29)	35.62(1.29)	35.16 (1.01)	.078
2–6 months	39.18(1.53)[¶]	38.77 (1.22)	36.99 (0.98)	.097

Values are presented as mean (SE), unless otherwise indicated.

[*] P values are calculated from the repeated measures analyses adjusting for body surface area.

[†] Cocaine versus no drugs at birth.

[‡] Cocaine versus other drugs at birth.

[§] Cocaine versus no drugs at 2 to 6 months.

[//] Cocaine versus other drugs at 2 to 6 months.

[¶] Significant change at 2 to 6 months of age from birth ($P < .015$).

Table III.

HR data according to the severity of cocaine exposure (observed means and standard errors)

	No cocaine	Light cocaine	Heavy cocaine	*P* *
Sample size (n)				
Birth	207	52	43	
2–6 months	165	36	35	
HR				
Birth	130.31 (0.62)	132.47(1.23)	134.40(1.37)	0.015†
2–6 months	142.47(0.70)//	141.53 (1.50)//	145.10(1.53)//	0.208
RMSSD				
Birth	21.65 (0.44)	21.11 (0.85)	19.37 (0.93)	0.048†
2–6 months	20.05 (0.35)//	23.43 (1.30)	20.43 (0.86)	0.017‡
SDNN				
Birth	47.25 (0.84)	43.67 (1.66)	39.72 (1.51)	0.002†
2–6 months	48.48 (0.72)	51.24(2.14)//	48.57(1.83)//	0.456
HF				
Birth	64.58 (3.61)	54.83 (5.99)	45.17(4.74)	0.013†
2–6 months	61.45 (3.35)	90.56(12.83)//	59.24(6.19)//	0.033‡
LF				
Birth	150.76(6.89)	129.16(11.31)	116.12(14.04)	0.038†
2–6 months	140.15 (6.40)	170.32(18.44)	128.65(14.18)//	0.185
Total				
Birth	1163.70 (57.85)	934.16(81.79)	803.04(87.31)	0.179
2–6 months	1160.84(80.98)	1309.84(135.16)	1134.03 (130.26)//	0.025§
VLF				
Birth	288.87(16.00)	246.79 (27.28)	256.55 (46.60)	0.478
2–6 months	246.34 (35.85)//	206.32 (24.78)	211.79 (33.72)	0.407
ULF				
Birth	659.33 (41.52)	530.26 (51.81)	406.40 (35.96)	0.187

	No cocaine	Light cocaine	Heavy cocaine	P^*
2–6 months	713.60 (44.59)	847.93 (97.52)	734.29 (85.75)//	0.014§
SNN-50				
Birth	5320.21 (319.81)	4738.43 (545.57)	3823.91 (600.47)	0.026†
2–6 months	4833.81 (324.20)	7579.70(1152.47)	5493.66 (782.17)//	0.022‡
SDNNI				
Birth	30.92 (0.65)	29.25(1.28)	26.00(1.22)	0.015†
2–6 months	28.74 (0.49)//	30.35(1.21)	28.83 (1.22)//	0.425
SDANN				
Birth	35.40 (0.83)	33.84(1.99)	29.53 (1.48)	0.043†
2–6 months	7.93 (0.79)	40.89 (2.56)//	37.37(1.54)//	0.180

Values presented as mean (SE) unless otherwise indicated.

*P values are calculated from the repeated measures analyses adjusting for body surface area.

†Heavy cocaine versus no cocaine at birth.

‡Light cocaine versus no cocaine at 2 to 6 months.

§No post-hoc pairwise differences were statistically significant at the adjusted alpha level of 0.017 (= 0.05/3).

//Significant change at 2 to 6 months of age from birth ($P < .01$).