The Effects of *In Utero* Cocaine-Exposure on the Heart Rate and Heart Rate Variability of Near and Full Term Infants following Orthostatic Stress

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Abstract

To understand the effects of in utero cocaine exposure on the developing fetus, we studied the heart rate and the heart rate variability (HRV) in near and full term cocaine-exposed infants during quiet sleep supine and following orthostatic stress. 21 cocaine-exposed and 23 control infants were studied within 120 hours of birth. 30-minute segments of the electrocardiogram (ECG) were recorded with the infant, horizontal followed by the infant in a 25° head-up tilt. The cocaine-exposed group, as compared with the control group, had a trend toward an increase in heart rate in the horizontal position and a significant increase in heart rate following the tilt. The frequency components of the heart rate were lower in the horizontal position and increased following the orthostatic stress. These results are consistent with the known pharmacological actions of cocaine and demonstrate the possible adverse neonatal effects of cocaine abuse during pregnancy.

1. Introduction

In 1999, an estimated 25 million Americans admitted that they had used cocaine at least once; 3.7 million had used it within the previous year; and 1.5 million were current users. Cocaine use by pregnant women has increased at an alarming rate in recent years. Prenatal cocaine use may lead to several perinatal complications [1]. Cocaine has important interactions with the autonomic nervous system that may be responsible for some of its adverse long-term effects [2]. Prenatal exposure to cocaine is also associated with abnormalities that may be observed shortly after birth and may persist through infancy, including increased neonatal stress behavior, motor development dysfunction and central nervous system irritability with electroencephalographic abnormalities [3].

Studies have documented significant behavioral effects of fetal cocaine exposure on attention abilities underlying auditory comprehension skills [5]. *In utero* cocaine exposure is believed to affect infant heart rate control. Studies have investigated these effects, and at times the conclusions conflict [6-9].

2. Methods

2.1. Subjects

We studied 23 control infants and 21 cocaine-exposed infants. The two groups were similar in birth weight and gestational age. All subjects were studied within 120 hours of birth. Cocaine exposure was determined by maternal self-report or neonatal toxicological urinalysis. The University of Tennessee and The University of Memphis Institutional Review Boards (IRB) approved this study and each participating mother gave a written informed consent.

2.2. Recording procedure

Two 30-minute segments of the electrocardiogram (ECG) were recorded; the first with the infant in the supine position and followed by the infant in a 25° head-up tilt position. All recordings were done on infants in the quiet sleep state as determined by observation of the infant. These ECG signals were digitized and R-R intervals were determined with 2 ms resolution.

2.3. HRV Analysis

We used three major approaches to HRV analysis **1.** Time domain analysis of HRV: (i) descriptive statistics and instantaneous variability (ii) Poincaré plots (iii) ΔRR_{n+1} vs. ΔRR_n plot. **2**. Non-Linear analysis of HRV: (i) approximate entropy (ApEn) (ii) fractal analysis **3.** Frequency domain analysis of HRV: (i) power spectral analysis and (ii) wavelet analysis. This method is based on the assumption that the time-series signal is a wide sense stationary signal. The LF region (0.02 to 0.2 Hz) was considered as a marker for both sympathetic and

parasympathetic activation. The parameters used were P_L/P_T ratio & LF wavelet coefficients. The HF region (0.2 to 2 Hz) was considered as a marker of parasympathetic activation. The parameters used were P_H/P_T ratio & HF wavelet coefficients.

3. Results

The mean heart rate in cocaine-exposed subjects was increased compared to control subjects. The number of points with two consecutive decreases in difference in R-R intervals compared to the points with two consecutive increases in difference in R-R intervals from the ΔRR_{n+1} vs. ΔRR_n plot was greater ($p = 0.016$) in cocaine-exposed subjects compared to control subjects ($p = 0.15$). The LF and HF wavelet coefficients from the wavelet analysis in cocaine-exposed subjects were decreased compared to control subjects although not statistically significant. The results from descriptive statistics, SDΔRR, non-linear analysis and frequency domain analysis did not indicate any statistically significant difference between the two groups in the horizontal position.

The mean heart rate in cocaine-exposed subjects increased following the tilt ($p = 0.014$). The results from SDΔRR, non-Linear analysis and frequency domain analysis did not indicate any statistically significant difference between the horizontal and incline positions in the cocaine-exposed group.

The P_L/P_T ratio from the power spectral analysis in control subjects was decreased following the tilt ($p = 0.023$) and the P_H/P_T ratio from the power spectral analysis was increased following the tilt ($p = 0.023$). The results from descriptive statistics, SDΔRR and non-Linear analysis did not indicate any statistically significant difference between the horizontal and incline positions in the control group.

4. Discussion

Our findings suggest that *in utero* cocaine exposure may alter heart rate dynamics in the postpartum period. The effects of *in utero* cocaine exposure on heart rate dynamics with orthostatic stress in near and full term infants have not been previously described.

The observed trend toward an increase in heart rate in the cocaine-exposed group compared to the control group in the horizontal position can be associated with the increased sympathetic nervous system activity after exposure to a sympathomimetic drug such as cocaine. The heart rate in the cocaine-exposed group was increased compared to the control group following the tilt. We know that orthostatic stress, tilting in our study, causes an increase in sympathetic activity due to the carotid baroreceptors and this leads to an increase in heart rate and cardiac output. This increase should be more pronounced in the cocaine-exposed infants due to the known sympathomimetic effect of this drug.

The number of points with two consecutive decreases in the difference in R-R intervals compared to the points with two consecutive increases in the difference in R-R intervals from the ΔRR_{n+1} versus ΔRR_n plot was significantly greater in cocaine-exposed subjects compared to control subjects This indicates an increase in sympathetic activity in cocaine-exposed infants compared to control infants. The decrease in P_L/P_T ratio and LF wavelet coefficients in cocaine-exposed infants compared to control infants in the horizontal position was not statistically significant in our study. Although the trend toward a decrease in P_L/P_T ratio was in agreement with a similar trend seen in preliminary studies by Oriol N *et al* [8]. The decrease in P_L/P_T ratio is also in agreement with the results from a study done by Garde *et al*, [14] also not statistically significant. In control subjects, the results from the power spectral analysis and the wavelet analysis showed a decrease in P_L/P_T ratio and also in LF wavelet coefficients even though not statistically significant. At the same time the P_H/P_T ratio showed an increase and there was also a similar in HF wavelet coefficients even though not statistically significant. A possible explanation based on the results from the power spectral analysis and the wavelet analysis can be that there is a more balanced parasympathetic and sympathetic activity following the tilt in the control subjects.

5. Conclusion

Our study has demonstrated that the heart rate in the cocaine-exposed group increased following the tilt whereas the control infants did not show a statistically significant increase. There was an observed trend that suggested an increase in sympathetic activity in cocaine-exposed infants in the horizontal position and also following the tilt. A larger sample size of 40 or more near and full term infants in each group could statistically demonstrate that the frequency domain effects of *in utero* cocaine-exposure in our study are consistent with the known pharmacological actions of this sympathomimetic drug and also its enhanced effect following orthostatic stress during the first 5 days of life. Our study does not address the question of whether these alterations are transient or if they are long-term effects implying alterations to the developing autonomic nervous system. Accordingly, long-term follow up of cocaine-exposed infants is essential to answer these questions.

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