Cocaine Effects on Neonatal Heart Rate Dynamics: Preliminary Findings and Methodological Problems

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Cocaine use by pregnant women has been reported to cause fetal and neonatal morbidity and mortality. We hypothesized that human neonates exposed to cocaine via maternal use during pregnancy might manifest changes in beat-to-beat heart rate variability, similar to those described in experimental animals. In this preliminary report, we present findings from the first systematic analysis of heart rate dynamics in a small group of (n = 5) neonates exposed in utero to cocaine compared to gestationally age matched controls (n = 6) without known drug exposure. Overall heart rate spectral power during ten minute periods of quiescent sleep was significantly reduced (p < 0.01) in the cocaine-exposed group, reminiscent of the changes recently reported in an animal model. In two other cocaine-exposed newborns, a quiescent sleep period could not be found. We discuss the special methodological problems associated with collection and interpretation of such data.

Cocaine use by pregnant women has increased at an alarming rate in recent years. Prenatal cocaine use may lead to placenta abruption, premature delivery, intrauterine growth retardation, congenital malformations, and fetal death [1–12]. 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 [13–17]. At present, however, we are unable to determine which newborns have had a pathophysiologic response to prenatal cocaine exposure and which are at risk for long-term effects.

In view of the public health implications of this widespread problem, a readily-employed, inexpensive, and non-invasive means of detecting and monitoring cocaine effects on neonates would be highly desirable. Cocaine has important neuroautonomic interactions which may be responsible for some of its adverse long-term effects [18, 19]. Neuroautonomic control of the cardiovascular system is reflected in beat-to-beat fluctuations in heart rate variability. Previous studies have demonstrated changes in heart rate variability in a variety of pathologic conditions characterized by altered neuroautonomic

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bAbbreviations used: ApEn, Approximate Entropy; ECG, electrocardiographic; EMIT, enzyme-multiplied immunoassay technique; FFT, Fast Fourier Transform; HR mean, heart rate mean; HRSD, heart rate standard deviation; PLF, power in low frequency band; PMF, power in medium frequency band; PHF, power in high frequency band; PT, total power.
function. Such changes may be detected by traditional measures of variability or by newer approaches based on spectral analysis and nonlinear dynamics [20–22]. Stambler et al. [23] recently reported that cocaine administration to experimental ferrets resulted in a marked decrease in sinus rhythm heart rate variability immediately prior to sudden death associated with seizures or ventricular arrhythmias. Heart rate variability data in human neonates exposed to cocaine in utero, however, has been limited.

In this report, we present preliminary findings from the first systematic analysis of heart rate dynamics in a small group of neonates exposed to cocaine compared to gestationally-aged matched controls. We also discuss the special methodological issues that make collection and analysis of such important data sets problematic and subject to potential misinterpretation.

METHODS

Subjects

Continuous ECG recordings were obtained from a total of 36 newborns, 10 of whom had been prenatally exposed to cocaine as determined by urine toxicological screening (see below). In order to be considered for analysis of heart rate variability, the following initial criteria had to be met: 1) ECG recording within 48 hrs of birth; 2) no known medical problems; 3) no medication known to affect the cardiovascular system. Subjects were included in the cocaine-exposed group only if their urine toxicological screen was positive for cocaine or its metabolites but negative for other drugs. A total of 7 of the 10 cocaine-exposed infants met these criteria. Two of these ten infants were excluded due to positive toxicological screens for other drugs, and one was excluded because the ECG was recorded 20 days after birth. For an infant to be considered as a control, there could be no medical suspicion of prenatal cocaine exposure. Therefore, these infants did not have toxicological screens performed. Control infants were selected with a range of gestational ages to overlap that in the cocaine group. A total of 6 control infants were identified.

Toxicological Screens

Urine samples were ordered solely at the discretion of the medical staff caring for the infants. The present study had no influence on the determination to order a toxicological screen or on the treatment of either the infants or their mothers. The major indications for screening were a positive history of maternal drug use or a lack of adequate prenatal care. Even in these settings, however, permission from the parent(s) had to be obtained for a screen to be performed. The samples were analyzed by standard EMIT for cocaine and its metabolites and for other drugs including opiates, phenothiazines, amphetamines, tricyclic antidepressants, ethanol, barbiturates, cannabinoids, benzodiazepines, and phenycyclidine.

Data Recording

Continuous recordings of ECG, 30–90 min in duration, were obtained from the neonates while they slept in a bassinet. The ECG was recorded onto a digital audio tape (TEAC RD-111T). Subsequently, the ECG signals were digitized at 500 Hz and stored on a digital computer (Macintosh II fx). QRS detection and beat classification were performed using an automated ECG analyzer [24] with visual verification.

Data Selection

It has been well documented that sleep state greatly affects heart rate variability in
infants [25]. Since it was not feasible to record electroencephalograms in this study, we compared similar, quiescent sleep periods from each infant using the technique of Harper et al. [25]. The median heart rate and the intraquartile heart rate range (i.e., the difference in heart rates between the values 12.5% above and below the median) were computed over sequential 1-min segments of data for the entire recording period. A single continuous data segment of 10 min duration, presumed to represent quiescent sleep, was chosen for further analysis based on the following criteria: 1) the segment was without ectopy, 2) median heart rate and variability were lower compared to other segments, and 3) there were no abrupt changes in either mean heart rate or variability.

An example of this analysis is shown in Figure 1 for one control infant and two cocaine-exposed infants. In the control and first cocaine-exposed infant, a quiescent sleep period is identifiable. Such a period is not clearly present, however, in the record of the second cocaine-exposed infant. Quiescent sleep periods could not be identified in 2 of the 7 cocaine-exposed infants who satisfied the initial screening criteria described above, and therefore their data were not used for comparison with controls.

**Heart Rate Dynamics**

A heart rate time series with equally-spaced samples was constructed from the sequence of R-R intervals using linear interpolation techniques at a sampling rate of 4 Hz. Heart rate variability was quantified on the 10 min data segments by means of the following indices. Mean heart rate and standard deviation of heart rate were calculated for each time series. Linear trends were then removed from the time series using standard linear regression techniques. The amplitude spectrum for each time series was computed using a FFT with a Hanning window. The amplitude spectrum was then smoothed with a 5 point moving average filter.

The power (sum of squared amplitudes) was calculated over a low frequency band (P_{LF}, 0.02–0.13 Hz), a medium frequency band (P_{MF}, 0.13–0.30 Hz), and a high frequency band (P_{HF}, 0.30–1.1 Hz) [26]. P_T was calculated as the sum over the three bands.

ApEn, a statistic derived from dynamical systems theory, was calculated to provide a single index of the overall “complexity” or “predictability” of each time series. The theoretical basis and computational details for ApEn have been presented by Pincus and colleagues [27–30]. Briefly, ApEn quantifies the regularity of the heart rate time series. The more regular and predictable the signal, the lower its value of ApEn. This measure may be applied to the output of deterministic (“chaotic”), stochastic, or “mixed” systems. In this study, ApEn was calculated over N = 2400 data points. The input parameters, m and r, were chosen to be 2 and 0.75, respectively. The value of r was chosen as 0.20 times the standard deviation of the heart rate time series averaged over all subjects as recommended by Pincus et al. [27–30].

**Statistical Methods**

Differences between control and cocaine-exposed infants were assessed by a two-tailed Mann-Whitney rank sum test. Level of significance was defined as $p < 0.05$.

**RESULTS**

Analysis of heart rate variability was performed in 11 infants during quiescent sleep: 6 control and 5 cocaine-exposed infants. There was no difference in the mean gestational age between the two groups (Table 1). The heart rate time series and amplitude spectra are shown in Figure 2 for all eleven infants. The results for all infants are summarized in Table 1.

Control and cocaine-exposed infants had similar mean heart rates. There were, how-
Figure 1. Min by min median heart rate and variability. The median heart rate and variability (defined as described in the text by intraquartile range) were calculated over 1-min intervals. Representative data are shown from a control infant (top panel) and for two cocaine-exposed infants (lower two panels). The quiescent sleep period for which heart rate variability analysis was performed is indicated by the segment between the arrows. Note that in the lower panel, a suitable 10 min quiescent period cannot be readily defined and, therefore, this subject was not included in the comparison with controls.

However, clear differences in the beat-to-beat heart rate variability between the groups. Decreased heart rate variability in the cocaine-exposed infants was evidenced by a significant decrease in $P_T$, resulting primarily from a reduction in $P_{LF}$; $P_{MF}$ and $P_{HF}$ were also reduced, but the changes did not achieve statistical significance. Heart rate standard deviation was also lower in the cocaine group, but this difference was not statistically significant. Of note, despite the wide range of gestational ages in both groups, only one control infant had a value of $P_T$ which overlapped the values observed in the cocaine-exposed group. ApEn of heart rate was also decreased in the cocaine-exposed infants, although the difference did not reach statistical significance.
Table 1. Heart rate dynamics.

| Subject | GA | HR_m | HR_SD | P_LF | P_MF | P_HP | P_T | ApEn |
|---------|----|------|-------|------|------|------|------|------|
| N1      | 32 | 134.6| 4.49  | 6.11 | 0.49 | 0.27 | 6.86 | 0.54 |
| N2      | 34 | 138.4| 3.85  | 4.62 | 0.54 | 0.36 | 5.52 | 0.60 |
| N3      | 33 | 121.1| 3.45  | 7.87 | 1.32 | 0.75 | 9.94 | 0.82 |
| N4      | 40 | 135.2| 4.55  | 4.22 | 0.50 | 0.14 | 4.86 | 0.54 |
| N5      | 37 | 125.1| 4.02  | 4.38 | 0.77 | 3.77 | 8.92 | 1.18 |
| N6      | 37 | 139.9| 2.77  | 2.93 | 0.28 | 0.51 | 3.72 | 0.66 |
| Mean    | 35 | 132.4| 3.86  | 5.02 | 0.65 | 0.97 | 6.64 | 0.72 |
| SD      | 3.0| 7.6  | 0.67  | 1.73 | 0.36 | 1.39 | 2.41 | 0.25 |
| C1      | 31 | 139.5| 1.96  | 1.23 | 0.02 | 0.05 | 1.30 | 0.25 |
| C2      | 31 | 138.5| 1.83  | 1.99 | 0.18 | 0.11 | 2.28 | 0.39 |
| C3      | 34 | 149.3| 2.40  | 1.68 | 0.25 | 0.29 | 2.22 | 0.43 |
| C4      | 39 | 122.2| 4.31  | 3.14 | 0.81 | 0.77 | 4.72 | 0.86 |
| C5      | 36 | 138.0| 3.38  | 3.33 | 0.68 | 0.50 | 4.51 | 0.60 |
| Mean    | 34 | 137.5| 2.78  | 2.27 | 0.39 | 0.34 | 3.01 | 0.50 |
| SD      | 3.4| 9.7  | 1.05  | 0.92 | 0.34 | 0.30 | 0.55 | 0.24 |
| p value |    |      |       |      |      |      |      |      |
| NS      | NS | NS   | NS (.08)| 0.02 | NS | NS | 0.02 | NS |

N, control infant; C, cocaine exposed infant; GA, gestational age (weeks); HR_m, mean heart rate; HR_SD, standard deviation of HR time series; P_LF, spectral power in low frequency band; P_MF, spectral power in medium frequency band; P_HP, spectral power in high frequency power; P_T, total spectral power; ApEn, Approximate Entropy; NS, not significant.

**DISCUSSION**

The effects of prenatal cocaine exposure on heart rate dynamics in the early neonatal period have not been described before. Our preliminary findings suggest that prenatal exposure to cocaine may alter heart rate dynamics in the early postpartum period. In particular, during quiescent sleep the cocaine-exposed infants showed a reduction primarily in low frequency heart rate variability versus controls.

**Mechanisms of Cocaine Effects on Heart Rate Dynamics**

The alterations in heart rate variability observed in the cocaine-exposed infants could be due to a number of factors including effects of cocaine upon the newborn's cardiovascular or autonomic nervous systems, mediated by direct toxicity or indirectly by repeated reductions in uterine blood flow that occur with acute maternal cocaine administration [31]. The reduced heart rate variability observed in the 5 infants for whom a quiescent sleep period could be identified is reminiscent of the results observed in conscious ferrets exposed to relatively high doses of cocaine [23]. While there were significant differences in the indices of heart rate variability between control and cocaine-exposed infants, there was no difference in the mean heart rate. The lack of effect of prenatal cocaine-exposure on mean heart rate in newborns has been reported by other investigators [32, 33]. A decrease in heart rate variability, quantified by spectral measures or ApEn, has been observed in a number of other conditions associated with altered neuroautonomic control, including congestive heart failure [20], myocardial infarction [21],
prior to sudden cardiac death [22], sudden infant death syndrome [34], and aging [28].

The observed decrease in heart rate variability in the frequency band generally associated with sympathetic nervous system activity, after exposure to a sympathomimetic drug like cocaine, appears paradoxical. It should be noted, however, that changes in heart rate fluctuations in the low frequency band cannot be considered as a simple index of directional changes in sympathetic "tone." Certain increases in sympathetic activation, such as those associated with acute anterior wall myocardial ischemia or baroreflex stimulation during tilting [35], do correlate well with increased low frequency spectral power. A sustained increase in sympathetic tone due to exercise, epinephrine infusion, or congestive heart failure, however, actually decreases these low frequency components of heart rate variability [36, 37]. Therefore, the spectral effects of cocaine-exposure in the present study are not inconsistent with the known pharmacological actions of this sympathomimetic drug.

These preliminary findings are consistent with other studies suggesting that alterations in central nervous system structure and function may be substantially perturbed by

Figure 2a. Heart rate dynamics. Heart rate time series and amplitude spectra for 6 control subjects.
Figure 2b. Heart rate time series and amplitude spectra for the 5 cocaine-exposed subjects during quiescent sleep. Spectral amplitude has units of (beats per min)/sec.

prenatal cocaine exposure [17, 38]. For example, prenatal cocaine may affect elements of the autonomic nervous system regulating respiration [38, 39, 40], temperature [38], and sleep cycles [38]. A link between prenatal cocaine exposure and sudden infant death syndrome has also been suggested [33, 38, 39], but this association remains controversial [41]. The lack of an apparent quiescent sleep period in two of the infants in this present study might reflect an altered sleep state associated with cocaine exposure. The hypothesis that cocaine exposure perturbs neuroautonomic control systems and that these effects are reflected by changes in beat-to-beat heart rate dynamics warrants further study. From a practical viewpoint, ECG time series analysis may provide a readily-employed method for quantitatively monitoring the effects of prenatal cocaine exposure.

Limitations

This preliminary investigation highlights a number of important methodological considerations that need to be addressed by future studies.
1) Heart rate variability in normal infants is greatly affected by multiple factors, including gestational age at birth, postnatal age, level of arousal, and sleep stage. In this study, we attempted to control for these factors by confining our analysis to data obtained during quiescent sleep in gestationally age-matched subjects.

2) A number of confounding factors, such as socio-economic and nutritional status and level of prenatal care, may bias the results of observational studies of this kind. No attempt was made to account for these factors; thus, we cannot assess their influence on the preliminary results reported here.

4) Toxicological screening of a neonate’s urine only provides an indication of recent in utero cocaine exposure, but gives no information concerning the dose, timing or chronicity of drug exposure.

5) Control infants did not have a toxicological screen. Therefore, it is possible that one or more of them could also have been exposed pre-natally to cocaine. This exposure, however, should have made the control and cocaine-exposed groups similar.

Clinical Implications and Future Studies

Our preliminary results suggest that abuse of cocaine by pregnant women just prior to delivery can alter neonatal heart rate dynamics. This finding raises the possibility that analysis of heart rate variability may help identify infants exposed in utero to cocaine, a group at risk for subsequent neuroautonomic and/or developmental abnormalities. A large scale study is needed to address the utility of heart rate monitoring in identifying and following these potentially high risk neonates, as well as in providing information on the effects of prenatal cocaine exposure on the development of autonomic control mechanisms.

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