Diastolic Filling Abnormalities by Color Kinesis in Newborns Exposed to Intrauterine Cocaine

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Because cocaine crosses the placenta, we prospectively evaluated global and segmental systolic and diastolic cardiac function by color kinesis in clinically asymptomatic newborns who were exposed to cocaine in utero (group 1, n = 82). Their data were compared with normal controls (group 3, n = 87) and newborns exposed to drugs other than cocaine (group 2, n = 108). During left ventricular filling, newborns exposed to cocaine, compared with groups 2 and 3, had significantly (\(P < .05\)) higher global fractional area change (%) (76 ± 10.3 vs 72 ± 9.4 and 72 ± 9.1, respectively), regional fractional area changes (%) for the anterior, septal, inferior, and lateral wall, and in the index of asynchrony (at 50% filling 13.2 ± 5.8 vs 11.3 ± 4.1 and 11.6 ± 4.2, respectively). There were no significant differences in systolic function among the 3 groups. Prenatal cocaine exposure in asymptomatic infants leads to higher global and segmental fractional area changes and asynchrony during diastole. The significance and course of these alterations require further investigation. (J Am Soc Echocardiogr 2002;15:447-53.)

Normotensive adults who are addicted to cocaine have left ventricular hypertrophy.\(^1\) In addition, cocaine addiction causes left ventricular (LV) systolic dysfunction, specifically lower ejection fraction and regional wall motion abnormalities.\(^2,3\) Short-term use also causes significant cardiac abnormalities. For example, cocaine infusion into the left coronary artery of adults compromises LV systolic performance by increasing end-systolic volume while decreasing the LV ejection fraction.\(^4\) The infusion also alters LV compliance by elevating end-diastolic pressures without a significant change in LV end-diastolic volume. Furthermore, it increases the systolic and mean arterial blood pressure without altering the heart rate or LV dP/dt.

Because cocaine readily crosses the placenta, it is possible that intrauterine exposure to cocaine may lead to similar cardiovascular abnormalities in the fetus and neonate. However, there is a paucity of data regarding LV function in infants born to mothers who use cocaine during pregnancy. In one report, infants with intrauterine exposure to cocaine had a lower cardiac output, lower stroke volume, and a higher blood pressure during the first day of life, as determined by Doppler echocardiography.\(^5\)

Approximately a third of the adults undergoing detoxification for cocaine addiction have ST segment changes,\(^6\) which may represent coronary artery spasm.\(^7\) Similar findings have been noted in asymptomatic newborn infants who had intrauterine cocaine exposure.\(^8\) It is possible that cocaine exposure leads to segmental wall motion abnormalities secondary to coronary artery spasm.

The purpose of this study was to determine whether intrauterine cocaine exposure is associated with systolic, diastolic, or segmental wall abnormalities in the neonatal myocardium. For this objective, we obtained and analyzed color kinesis images in cocaine-exposed neonates and in noncocaine-exposed infants. Two-dimensional echocardiography provides a subjective and qualitative method for assessing segmental wall motion abnormalities, which may be affected by interobserver and intraobserver error. Color kinesis provides a real-time, color-coded display of LV endocardial motion, which enables an objective method for quantifying LV segmental wall motion.\(^9\)

METHODS

Infants were eligible for the study if they were less than 48 hours old, weighed more than 1500 g, and were between 33 and 42 weeks gestation. Infants were excluded if they had any significant medical problems (for example, receiving any medica-
tions including supplemental oxygen, birth asphyxia with 5-minute Apgar <6; any illicit drug exposure in utero, excluding alcohol, marijuana, cocaine, and nicotine; and any significant maternal surgical or medical problems requiring pharmacologic treatment (eg, hypertension, depression, asthma). Newborns with associated congenital anomalies, including cardiac defects (except patent ductus arteriosus, patent foramen ovale or physiologic mitral, tricuspid, or pulmonary regurgitation) were also excluded.

We used a convenience sampling strategy with the goal of enrolling 2 controls for each cocaine-exposed infant. Because cocaine-exposed infants (group 1) were likely to be exposed to other drugs in utero, especially alcohol, marijuana (THC), and/or nicotine, the first control group consisted of infants with exposure to alcohol, THC, and/or nicotine (group 2). The second control group had no intrauterine drug exposure (group 3).

**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, cannabinoids, opiates, phencyclidine, amphetamines, and cotinine. The samples were first screened by the Enzyme Multiplied Immunoassay Technique (EMIT). If the urine sample was positive, the result was then confirmed by thin-layered chromatography using 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 benzoylecgonine, and m-OH-benzoylecgonine with the addition of coca-ethylene in the meconium. Infants and their biologic mothers were seen as soon as possible after birth, at which time the caregiver was interviewed regarding drug abuse. An adaptation of the Maternal Post-Partum Questionnaire 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 oz 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. 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. The remaining cocaine-exposed infants were defined as having a light cocaine exposure. 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 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/parents of all participants.

**Color Kinesis**

All infants underwent echocardiography and Doppler studies including color kinesis (Figure 1) with a 5-MHz transducer (SONOS 5500 Ultrasonograph, Hewlett-Packard, Andover, Mass) by an experienced pediatric-trained sonographer. In contrast to adults, in whom delineation of the endocardium may be difficult, we had optimal delineation of the endocardial surface of the left ventricle in all infants. In our pilot study, the parasternal short-axis view in infants had more consistent landmarks than the apical 4-chamber view. In addition, the parasternal short-axis view in infants is easier to acquire with higher reproducibility. In adults, there is greater intersubject

![Figure 1 Color kinesis images from a newborn during systole (A) and during diastole (B).](image-url)
variability in the 4-chamber view in contrast with the short-axis view. In addition, MRI studies have shown less rotational error in the parasternal short-axis view than in the 4-chamber view. For these reasons, the parasternal short-axis view, at the level of the papillary muscles, was used for the color kinesis studies. Color kinesis images were analyzed offline by a cardiologist trained in color kinesis who was blinded to the infant’s drug exposure status. The analysis was performed with automated software (Quick Color Kinesis, EchoSoft Co, Wilmington, Del). The LV end-systolic and diastolic cavity was segmented into six 60-degree, wedge-shaped segments (clockwise: anterior, lateral, posterior, inferior, septal, and anteroseptal segments). The centroid and a manually determined anatomic landmark at the junction of the right ventricular posterior wall endocardium and the interventricular septum defined the zero line for the segments. Incremental area change was normalized from the end-diastolic area of the corresponding segment, resulting in regional fractional area change (%) during systole and diastole. We analyzed global and regional, systolic and diastolic parameters. The following diastolic parameters were measured: early peak filling rate, early filling duration, ratio of peak velocity of early (E wave) and late (A wave) diastolic mitral flow (E/A), end-diastolic area (EDA), global fractional area change during filling (GFAC), and index of asynchrony. The index of asynchrony (IA) for LV filling was calculated as the standard deviation of the mean percent of filling of all segments at 50% filling time. The global fractional area change was calculated by dividing the incremental area change by the end-diastolic area. The segmental fractional area change (%) for each segment was calculated by dividing the incremental area change of that segment by its end-diastolic area. Similar variables were measured for global and regional systolic function. A complete echocardiographic study (including M-mode, 2D, and Doppler) was performed at the same time with careful attention to the gain and filter settings to obtain clear images from endocardial and epicardial surfaces.

Data were analyzed with the statistical software SAS V.8.0 (SAS Institute Inc, Cary, NC). Hypothesis testing regarding group differences was tested by using analysis of variance. Because early peak filling rate, early filling duration, and E/A were correlated with mean heart rate, analysis of covariance was used controlling for mean heart rate for these variables. Post hoc comparisons were adjusted by Bonferroni corrections. Distributional assumptions were assessed to test for appropriate underlying assumptions. Raw means, percentages, and standard deviations are reported. Statistical significance was defined a priori as a P value < .05, 2-tail.

**RESULTS**

Two hundred seventy-seven asymptomatic infants who were less than 48 hours old were enrolled. On the basis of history (self-reporting) and toxicology studies, mothers of the 82 cocaine-exposed infants (group 1) also used alcohol (69%), marijuana (35%), and nicotine (91%), whereas mothers in the first control group (group 2, n = 108) used alcohol (43%), marijuana (27%), and nicotine (70%) but no cocaine. The second control group (group 3 no drugs, n = 87) was free of all drugs. The patient characteristics for these 3 groups are reported in Table 1. As noted in other studies, cocaine-exposed infants at birth had lower gestational age, birth anthropometrical measurements (weight, length, head circumference), and 1-minute Apgar score. Mothers who used cocaine were older and had less education, fewer prenatal visits, more pregnancies, and more pregnancy losses than the other 2 groups. Among all 3 groups, Apgar score at 5 minutes and socioeconomic status were similar.

Compared with the 2 control groups, during diastole, cocaine-exposed infants had higher index of asynchrony, global (GFAC), and segmental (anterior, lateral, inferior, and septal) fractional area changes (Table 2). GFAC changes reflect percent area changes from end-diastolic area (EDA), whereas regional area changes reflect percent area changes from regional end-diastolic areas (REDA). The differences in index of asynchrony during diastole were more pronounced in infants exposed to heavy in utero cocaine (Table 3). There were no differences among the 3 groups for systolic parameters, volume changes, ejection fractions, and shortening fractions.

**DISCUSSION**

With the help of color kinesis, we have observed alterations in diastolic filling, including increased index of asynchrony, in newborns exposed to in utero cocaine. In adults, increased index of asynchrony signifies diastolic dysfunction. Furthermore, the degree of abnormality in the index of asynchrony was greater in newborn infants with a heavier cocaine exposure.

The role of color kinesis in the study of qualitative and
These patients had lower filling fractions, lower ratios of peak filling rate/heart rate, and mean filling time/RR. Quantitative analysis of color kinesis images was also used to identify diastolic dysfunction in 25 patients with cardiac hypertrophy whose systolic function was preserved. In addition to decreased filling seen during the first half of diastole, these subjects had increased index of asynchrony with wide intersegmental variability in the regional LV filling times. Index of asynchrony was even higher among patients with coronary artery disease who had mitral valve regurgitation.

Our findings of increased index of asynchrony in...
heavily cocaine-exposed infants is consistent with the reported finding of diastolic filling abnormalities noted in adults with left ventricular hypertrophy and coronary artery disease. Recently, increased diastolic chamber stiffness during demand ischemia (angina) has been linked to high-energy phosphate depletion and or increase in ADP. Non-uniformity in temporal and regional distribution of load and inactivation is one of the major factors influencing LV relaxation. Diastolic wall motion asynchrony may be related to uneven myocardial hypertrophy, localized foci of interstitial fibrosis, and non-uniform loss of contractile elements. Our subjects did not have LV hypertrophy or obvious systolic wall motion abnormalities. The possibility of uneven myocardial hypertrophy, non-uniform loss of contractile elements or localized foci of interstitial fibrosis cannot be confirmed or refuted from the current studies. Scattered foci of myocardial necrosis and fibrosis have been noted in adults among cocaine users.

Contrary to lower filling fractions expected in subjects with impaired diastolic function, cocaine-exposed infants had increased global and regional filling fractions. These findings are similar to inotropic effects seen after dobutamine infusion. In the absence of significant alterations in the cardiac output or systolic function, the significance of these findings or the mechanisms involved in this process remain unclear. Altered segmental filling fractions are more consistent with regional involvement of the myocardium with the possible relationship to coronary artery involvement. This is different from the global involvement seen in cardiomyopathy. Whether these segmental findings are part of global changes or represent a unique reaction of the developing myocardium (with the ability for hyperplasia rather than hypertrophy) to cocaine exposure remains speculative. Regional diastolic LV filling abnormalities are sensitive early signs of myocardial ischemia and may occur with normal systolic function. Preserved LV systolic function suggests an early or mild process that may be related to coronary artery spasm rather than infarction.

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. A random selection of 100 women with positive urine toxicology or history of cocaine use during pregnancy were older, with significantly more prior pregnancies and pregnancy losses than non-cocaine users, even with maternal age controlled. Alcohol, marijuana, and cigarette use were significantly higher. They also received less prenatal care and their infants had lower delivery weights for height. Infants of cocaine users had significantly smaller birth weights, lengths, and gestations—with 40% born preterm. In addition, the incidence of low birth weight (<2500 g) was significantly higher (33% vs 14%, P < .01). None of the demographic differences were significantly related to our echocardiographic parameters.

There are 3 potential limitations in interpreting the increased global and regional fractional area changes in our study. First, fractional area changes do not necessarily reflect volume changes or the cardiac output. These are area changes only. Second, these fractional area changes were measured only in the short axis and may or may not be reflective of changes in the long axis or in other LV dimensions. Third, the possible contribution of LV rotational changes to our measurements of global or regional fractional area changes during the relaxation period cannot be estimated by the current noninvasive methods. We expect this distortion to be minimal because similar rotational changes probably occurred in the control population. Furthermore, based on diastolic biomechanics of 11 healthy infants (2-11 months), apical walls do the most rotation and septal walls at each short-axis level undergo the least radial wall motion. The concerns regarding temporal resolution, not being high enough for accurate measurements of the endocardial velocity rates at high heart rates seen in our subjects, are not applicable to our data of fractional area changes or index of asynchrony.

In this study, color kinesis parameters were measured only in the parasternal short-axis view. Therefore, it is possible that we missed certain abnormalities of systolic and diastolic function, particularly at the apex of the left ventricle. Furthermore, segmental wall motion abnormalities of other LV segments, which could be seen only in other views, may have also gone undetected.

Our study has several advantages that may have increased the likelihood of detecting significant drug effects. Maternal drug status was determined through both biologic (meconium and urine screen) and clinical means enhancing reliability of classification. Although self-report of drug use may have some degree of unreliability, the use of the combined measures to determine heavier versus lighter exposure has been demonstrated in other studies to increase accuracy of data. Moreover, in similar samples of cocaine-using mothers using the same assessment interview and meconium assays, biologic measures were confirmatory of self-report, supporting the validity of the classification of exposure in this sample.

Whether cardiac alterations observed in our study contribute to cardiovascular morbidity or mortality is unknown. An earlier study reported 18 prenatally cocaine-exposed infants having sustained arrhythmias leading to congestive heart failure, cardio-respiratory arrest, and death.

Intrauterine cocaine exposure has been associated
with a 3- to 8-fold increase in sudden infant death in contrast to those who were not exposed to cocaine (4.62 per 1000 vs 1.39 per 1000, 8.36 per 1000 vs 1.22 per 1000, 9.3 per 1000 vs 1.3 per 1000). Because the natural history of cocaine-induced cardiac effects in infants is unknown, it is crucial that these infants and children are monitored closely for untoward cardiac events. Only long-term studies will reveal whether these children are more prone to develop coronary artery arteriosclerosis or have less cardiac reserve in response to stress than the general population.

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REFERENCES


