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Bradycardia as a Marker of Chronic Cocaine Use: A Novel Cardiovascular Finding

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Abstract

Background—Few studies have examined the effects of chronic cocaine use on the resting surface electrocardiogram (ECG) between exposures to cocaine.

Methods—12-lead ECGs from 97 treatment-seeking cocaine-dependent subjects were compared to ECG parameters from 8513 non-cocaine-using control subjects from the Atherosclerosis Risk in Communities study.

Results—After matching and adjusting for relevant covariates, cocaine use demonstrated large and statistically reliable effects on early repolarization, bradycardia, severe bradycardia, and heart rate. Current cocaine dependence corresponds to an increased odds of demonstrating early repolarization by a factor of 4.92 and increased odds of bradycardia and severe bradycardia by factors 3.02 and 5.11, respectively.

Conclusion—This study demonstrates the novel finding that long-lasting effects of cocaine use on both the cardiac conduction and the autonomic nervous system pose a risk of adverse cardiovascular events between episodes of cocaine use, and that bradycardia is a marker of chronic cocaine use.

Keywords

cocaine dependence; bradycardia; early repolarization

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Introduction

Cocaine is a powerfully addictive central nervous system stimulant that is commonly used in the United States. The National Institute on Drug Abuse (NIDA) reports that in 2009, 4.8 million Americans age 12 and older used cocaine in any form and 1.0 million had used crack cocaine at least once in the year prior to being surveyed¹. Cocaine is known to play a causal role in several cardiovascular complications including acute coronary syndromes, accelerated atherosclerosis, aortic dissection, endocarditis, myocardial dysfunction, and dysrhythmias^{2,3}.

Several cardiac dysrhythmias related to cocaine have been documented³. These include sinus tachycardia, supraventricular tachycardia, bundle branch block, complete heart block, ventricular tachycardia, ventricular fibrillation, asystole, and torsades de pointes. Most studies have focused on the association between acute cocaine use and the occurrence of ventricular arrhythmias (such as monomorphic VT) and QT prolongation⁴⁻⁸. Dysrhythmias associated with acute cocaine use may be related to sodium and potassium channel blockade, thus prolonging both conduction and repolarization³. In addition to its effects on sodium channels, cocaine enhances sympathetic drive, which increases ventricular irritability and promotes ventricular tachyarrhythmias. However, the exact mechanism of action and arrhythmogenic potential of chronic cocaine use has not been well documented in human electrophysiologic studies⁹.

To date, there has been one smaller human study that focused specifically on the relationship between chronic cocaine use and sinus bradycardia adjusting for age and gender¹⁰. That study found that habitual cocaine use was associated with a significantly increased incidence of sinus bradycardia when compared with controls. Whereas bradycardia may produce clinical symptoms, such as fatigue that might contribute to withdrawal symptoms, it is also a known risk factor for the development of certain types of ventricular arrhythmias^{11,12}.

Sinus bradycardia has also been associated with the common electrocardiographic finding of early repolarization^{13,14}. Early repolarization affects 1–5% of the general population and was long considered to be a benign condition^{13,14}. However, recent clinical studies have shown that patients with this type of ECG pattern are at increased risk of ventricular fibrillation (VF)^{15,16}.

The objective of this study was to examine resting electrocardiograms of chronic cocaine users for abnormalities, and to compare these ECG parameters to those of non-drug using controls. Accordingly, the analysis was restricted to subjects without cardiac symptoms and ECGs obtained in the absence of acute cocaine intoxication. The relationship between cocaine use, sinus bradycardia, and early repolarization in cocaine users was also examined.

Methods

Patient Population

We retrospectively reviewed the ECG recordings taken from August 2006 through December 2010 in 244 cocaine-dependent subjects. These ECGs were collected as part of a

screening process prior to entry into research studies within the Center for Neurobehavioral Research on Addictions at the University of Texas Health Center at Houston. Patients showed no symptoms of cocaine intoxication at the time of ECG recording. All patients were screened by licensed clinical counselors for symptoms of cocaine dependence as defined by the Diagnostic and Statistical Manual of Mental Disorders version IV text revision (DSM-IV-TR) using the Structured Clinical Interview for the DSM Disorders (SCID)¹⁷. Subjects who met DSM-IV-TR criteria for cocaine dependence in between the ages of 45–60 years old were included. Those with concomitant illicit opiate, benzodiazepine, amphetamine or methamphetamine use, as verified by serial urine toxicology testing, were excluded. Concomitant marijuana and alcohol use was not exclusionary as the majority of treatment-seeking cocaine dependent patients also use these drugs. Cocaine dependent subjects who had documented previous myocardial infarction, diabetes, or medications (including antihypertensive medications) that could affect the central or peripheral nervous system were also excluded. This retrospective chart review evaluated existing data collected as part of the screening protocol that was reviewed and approved by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Medical School, Houston.

In addition, de-identified electrocardiographic data from 8513 control subjects were reviewed. This data was provided from the Atherosclerosis Risk in Communities (ARIC) study funded by the National Heart Lung and Blood Institute (NHLBI) at the National Institutes of Health. Subjects were randomly selected from the 15,732 subjects in the dataset to approximate the age, gender, race distribution of the cocaine dependent subjects. In addition, subjects coded in the NHLBI dataset as having a previous myocardial infarction, diabetes, and medications for hypertension were excluded.

Cocaine-dependent subjects ranged in age from 20–60 and control subjects in the ARIC dataset ranged in age from 45–65. To avoid bias due to differences in age distribution between the cocaine and control subjects, primary analysis for the current study restricted the age range to subjects aged 45–60¹⁸. See Figure 1.

ECG Analysis

Standard 12-lead electrocardiograms were recorded at a speed of 25 mm/s and voltage of 10 mm/mV in an outpatient psychiatric clinic setting. These ECGs were reviewed by two independent and experienced cardiologists. The following parameters were identified: heart rate, rhythm, PR interval in milliseconds (ms), QRS interval in milliseconds, QT interval in milliseconds, QT corrected interval in milliseconds, presence or absence of early repolarization, presence or absence of left ventricular hypertrophy (by Cornell and Estes criteria)^{19,20}, and presence or absence of ST segment elevation consistent with Brugada criteria^{21,22}. Sinus bradycardia was defined as a heart rate < 60 beats per minute (bpm). Severe bradycardia was defined as < 50 bpm. Early repolarization was defined as an elevation of the J point 1mm compared to the baseline accompanied by a positive T wave with upward concavity in at least two adjacent leads^{13,14}.

Of note, the ARIC database did not include QT or QTc data for approximately 14,000 subjects. Therefore, QT and QTc data is not reported for control subjects from this database.

However, normal QT and QTc measurements in the general population are extensively described in the literature^{22,23}. In general, a normal QTc measurement is considered to be acceptable if it is less than or equal to 440 ms.

Measurements of Cocaine Use

Cocaine dependent subjects provided information regarding duration of cocaine use (years) and frequency of recent use (days in past 30). They also underwent a urine drug screen for the cocaine metabolite benzoylecgonine (BE). Self-reported cocaine use was not available for eight cocaine dependent subjects. Urine drug screen results were not available on 35 subjects.

Statistical Methods

A Student's t-test was used to compare continuous variables and Chi-Square analysis or a Fisher's exact test was used to compare categorical variables. *P* values of < 0.05 were considered statistically significant.

Following Stuart and Rubin's recommendation for "doubly robust" estimation¹⁸, the current protocol implemented matching followed by covariate adjusted estimates for the effect of cocaine use on cardiac variables. Propensity score matching reduced bias by matching control subjects and cocaine subjects on baseline covariates. Six different matching algorithms (exact, nearest neighbor, optimal, full matching, genetic matching, and coarsened exact matching) evaluated the balance across cases and controls on the following covariates: age, gender, ethnicity, former drinker, current drinker, former smoker, current smoker, education level, total cholesterol level, triglycerides, and BMI. Inclusion of grand mean single imputation with the addition of a missingness vector for salient covariates addressed missing observations. Inspection of the absolute standardized differences in means between the matched control and matched treatment group for each covariate suggested that full matching minimized differences across groups as well as extreme values for all covariates. Regression analysis on the matched samples, with a model including the same covariates used for matching, adjusted for any remaining covariate differences. Regression analysis of the early repolarization outcome also adjusted for heart rate.

Results

Of the 244 cocaine users' electrocardiograms reviewed, 93 patients (38%) were excluded due to age outside the range of 45–60 years old, and 54 patients (22%) were excluded due to concomitant medical or psychiatric history. 97 cocaine-dependent subjects and 8513 control subjects were included in the final analysis. The baseline characteristics and electrocardiographic data of all 8610 patients are presented in Table 1. The two groups differed significantly on gender or ethnicity ($p < 0.0001$ and $p < 0.0001$, respectively). Mean age among cocaine-dependent subjects was 49.5 ± 3.9 years and was 51.8 ± 4.5 years in control subjects ($p < 0.0001$). The mean QT interval of female cocaine users was 417.3 ± 37.7 ms and mean QT interval of male cocaine users was 420.5 ± 33.1 ms. (QT corrected (QTc) interval was $420.6.1 \pm 16.3$ ms in female cocaine users and 409.8 ± 14.8 ms in male

cocaine users. 1 % of both controls and cocaine users' ECGs met criteria for left ventricular hypertrophy. No QRS or ST segment changes were consistent with the Brugada syndrome.

ECG measured heart rates were significantly lower in cocaine-dependent subjects than in controls (Figure 2). Mean heart rate was 58.9 ± 9.8 bpm for cocaine users and 66.2 ± 9.6 bpm for controls ($p < 0.0001$). The proportion of subjects with heart rates below 60 bpm was significantly higher for cocaine-dependent subjects, with 59.8% of cocaine-dependent subjects having bradycardia, compared to 23.9% of controls ($p < 0.0001$). Likewise, the proportion of cocaine dependent subjects with severe bradycardia (ECG heart rate < 50 bpm) was significantly higher in cocaine-dependent subjects (22.7%) compared to controls (3.5%) ($p < 0.0001$).

Within cocaine-dependent subjects, 27.8% of subjects had early repolarization. Rates of early repolarization tended to be higher in cocaine-dependent subjects with bradycardia (34.5%) compared to cocaine-dependent subjects without bradycardia (18.0%) (Pearson Chi-square = 3.17, $p = 0.075$). Differences in rates of early repolarization were even stronger in cocaine-dependent subjects with severe bradycardia (45.5%) compared to those without severe bradycardia (22.7%) ($p = 0.036$). Of those with early repolarization findings, criteria were evident in the lateral leads in 14 (52%) and in inferior leads in 2 (7%). Global criteria (inferior, lateral and right precordial leads) were evident in 21 (41%).

The adjusted effect size estimates of early repolarization, bradycardia, and severe bradycardia for cases relative to controls are listed in Table 2. After matching and adjusting for relevant covariates, cocaine use demonstrated large and statistically reliable effects on early repolarization, bradycardia, severe bradycardia, and heart rate. Current cocaine dependence corresponds to an increased odds of demonstrating early repolarization by a factor of 4.92 (95% CI 2.73–8.87), adjusting for heart rate and by a factor of 5.58 when not adjusted for heart rate (95% CI 3.13–9.94). Cocaine dependence is associated with an increase in the odds of bradycardia and severe bradycardia by factors 3.02 (CI 1.95–4.66) and 5.11 (95% CI 2.95–8.84), respectively. Finally, cocaine dependence is associated with a decrease of 5.84 bpm in resting heart rate (95% CI 7.85–3.82). Finally, we re-ran the analyses on the total cocaine sample including the full age range (20 – 60 years old). Although the matching procedure failed to produce adequate covariate balance due to the disparity in age range between the groups, the same set of results obtained, with cocaine dependence associated with significant effects on heart rate, bradycardia, severe bradycardia and early repolarization. Since the matching procedure performed poorly for the full age range analysis (cocaine group: ages 20–60), the age restricted analysis (cocaine group: ages 45–60) reported above provides the most unbiased estimates.

There was no relationship between presence of the cocaine metabolite BE in urine and heart rate. Cocaine dependent subjects who were positive for BE had a mean heart rate of 58.8 ± 10.3 bpm, while those were negative for the metabolite had a mean heart rate of 58.6 ± 8.5 bpm ($t = 0.07$, $p = 0.9477$). Likewise, BE status was not related to bradycardia, severe bradycardia, or early repolarization. There was a significant association between years of cocaine use and presence of severe bradycardia, even after controlling for age. Subjects with

severe bradycardia reported more years of cocaine use (20.1 years) compared to subjects without severe bradycardia (15.4 years), $p=0.011$.

Discussion

Overall, the main findings of our study are threefold. First, we found that ECG measured resting heart rate is significantly lower in chronic cocaine users compared to control subjects. Secondly, cocaine users had much higher odds of ECG changes consistent with early repolarization compared to controls (see figure 3 for sample ECG tracing). Though higher rates of early repolarization were found in cocaine users with bradycardia, regression analysis shows that cocaine-dependent subjects have elevated odds of early repolarization relative to matched controls even after controlling for heart rate. Finally, our data shows that severity of bradycardia is associated with greater length of cocaine use, but not related to recency of cocaine use as measured by urine BE (urine BE will typically be positive 48 hours after cocaine use, but has been shown to detect use up to 88 hours prior²⁴).

To date, there have been two other human studies examining the relationship between chronic cocaine use and heart rate between episodes of use^{10,25,26}. Comparing 54 cocaine users to 54 gender-matched controls admitted to the ED, Hollander et al. found that cocaine users had higher heart rates²⁵. In contrast, Fontaine et al. compared 160 habitual cocaine users to 160 age and gender-matched controls admitted to the ER, finding that cocaine users had higher rates of sinus bradycardia relative to controls¹⁰. One preclinical study found that rodents treated with intraperitoneal cocaine 20mg/kg/day for 14 days could not mount an appropriate tachycardic response to acute blood loss and hemorrhagic shock when compared to controls²⁷. In addition, chronic cocaine use can blunt the body's normal adrenergic response to stress and has been linked to decreased survival²⁷. Cocaine's potent effect on the autonomic nervous system likely contributes to the high rates of sinus bradycardia seen in both studies. During acute use, cocaine blocks the presynaptic reuptake of norepinephrine and dopamine, producing an excess of these neurotransmitters at the postsynaptic receptor site, acting as a sympathomimetic agent³. Previous studies have shown that continuous exposure to catecholamines leads to β -adrenergic receptor desensitization^{28,29}. Here, we define desensitization as a diminishing biologic response during continuous exposure to a stimulus.

Schwinn et al³⁰ showed that cardiopulmonary bypass, a known powerful stimulant of endogenous catecholamine release, leads not only to myocardial β -adrenergic receptor desensitization, but also to a decrease in receptor density. We hypothesize that a similar mechanism of action explains why over half of cocaine users in our study are bradycardic, and why severity of bradycardia is associated with length of cocaine use. It is likely that repeated exposure to cocaine eventually leads to myocardial β -adrenergic receptor down-regulation, and thus slower heart rates. Our data also shows that heart rate down-regulation, and presumably β -receptor down-regulation, appear to outlast the urine BE test, however the time course of recovery remains to be determined. Another possible mechanism of action is the myopathy and diffuse myocardial necrosis associated with chronic cocaine abuse²⁶, which could occur throughout the conduction system to produce the observed sinus

bradycardia. It is possible that symptoms of bradycardia during withdrawal contribute to the addictive nature of cocaine.

Two prior studies^{31,32} showed that cocaine dependent subjects who were admitted to the hospital showed a significant increase in heart rate over the first week after abstaining from cocaine use in a small number of individuals. The results of these studies suggest that longer term abstinence from cocaine might ameliorate bradycardia. This has implications for treatment research as resolving bradycardia could be pursued as a diagnostic marker of long term abstinence.

Early repolarization has been referred to as a “J wave syndrome linked to abnormalities of the transient outward current (I_{to}), seen in ventricular epicardium. While initially thought to represent a benign ECG finding, increasing evidence indicates that early repolarization can be associated with increased risk for VF and sudden cardiac death^{15,16}. The ECG leads involved, magnitude of the J wave, and degree of ST elevation appear to be key determinants of whether or not early repolarization will lead to a lethal rhythm. Antzelevitch et al³³ suggested that patients with type 3 early repolarization, those with global early repolarization as seen in the lateral, inferior, and right precordial leads, are at the highest risk for ventricular dysrhythmias. In this study, over 40% of all cocaine users with early repolarization presented with ECGs consistent with type 3 early repolarization.

While the prevalence of early repolarization in the general population varies between 1–5%^{13,14}, some specific populations have been shown to have higher rates of this ECG finding. It has more commonly been seen in men and young persons (up to 27.5%)³⁴. Earlier studies intimated that early repolarization was more likely to be seen in African Americans, but contemporary studies have challenged this concept³⁴. One study of 56 active cocaine users that presented to the emergency room for treatment of chest pain were found to have high rates of early repolarization, between 32–41%, on initial ECG²⁵. Our study corroborates this finding, demonstrating a slightly more modest effect in the subacute setting.

The extent of ST-segment elevation as seen in early repolarization is affected by several well documented factors, including heart rate, medications, and autonomic influence. Slowing of the heart rate increases ST-segment elevation, as seen with β receptor blockade, while an increase in heart rate, as seen after isoproterenol administration or during exercise, often eliminates the ST-segment elevation³⁴. We suspect that a large percentage of cocaine users were bradycardic due to myocardial β -adrenergic receptor desensitization and down-regulation, resulting in blunted adrenergic effect. This is the most likely explanation for our study’s finding of increasing rates of early repolarization among those cocaine abusers with more profound bradycardia. Of note, only 1% of cocaine users met criteria for left ventricular hypertrophy, so this did not likely contribute to our study’s finding of high rates of early repolarization.

Cocaine’s effects on neurotransmitters and sodium channel blocking properties are well known. Our study did not show an increase in either QRS or QT intervals beyond accepted norms in these chronic cocaine users. However, the effects on sodium channels may

contribute to the high rates of early repolarization seen. Sodium channel blockers have been reported to increase ST-segment elevation in patients with early repolarization³⁴.

Our study has several limitations. First, the observational nature of this retrospective study restricts causal inference. Secondly, although 244 number cocaine abusers' electrocardiograms were screened, only 97 patients were included in our analysis, due to exclusion of subjects with concomitant drug use, cardiac history, or age that did not overlap with the control subjects. The effect of polysubstance abuse deserves further investigation. Future research should focus on recruiting larger numbers of patients with prospective ECG evaluation. There was also the smaller issue of urine drug screen results not being available for 10 patients. The coarse nature of urine drug screen results and underreporting in self-report measures³⁵ prevents more fine-grained assessment of the effect of time since last use. It should also be noted that the majority of our cocaine subjects were African American men. Future studies should focus on a more diverse subject population to determine whether our results can be extended to other ethnicities and to women. Finally, we were not able to obtain long term follow up regarding major adverse cardiac events, specifically on sudden cardiac death. It would be important to know if patients with these ECG changes did have higher rates of ventricular arrhythmias, or if they have a relatively benign course as some population studies of early repolarization have suggested. Future studies should focus on assessing the long-term cardiac outcomes of chronic cocaine users and assessing whether abstinence from cocaine improves severity of bradycardia.

The results of this study demonstrate the novel finding that severe bradycardia may be a marker of chronic cocaine use. Additionally, within cocaine users, severity of bradycardia is linked to higher rates of early repolarization, potentially increasing risk of sudden cardiac death in between episodes of acute cocaine use. Finally, severity of bradycardia is related to chronicity of cocaine use.

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Appendix A

Analysis including all cocaine subjects aged 20 to 60.

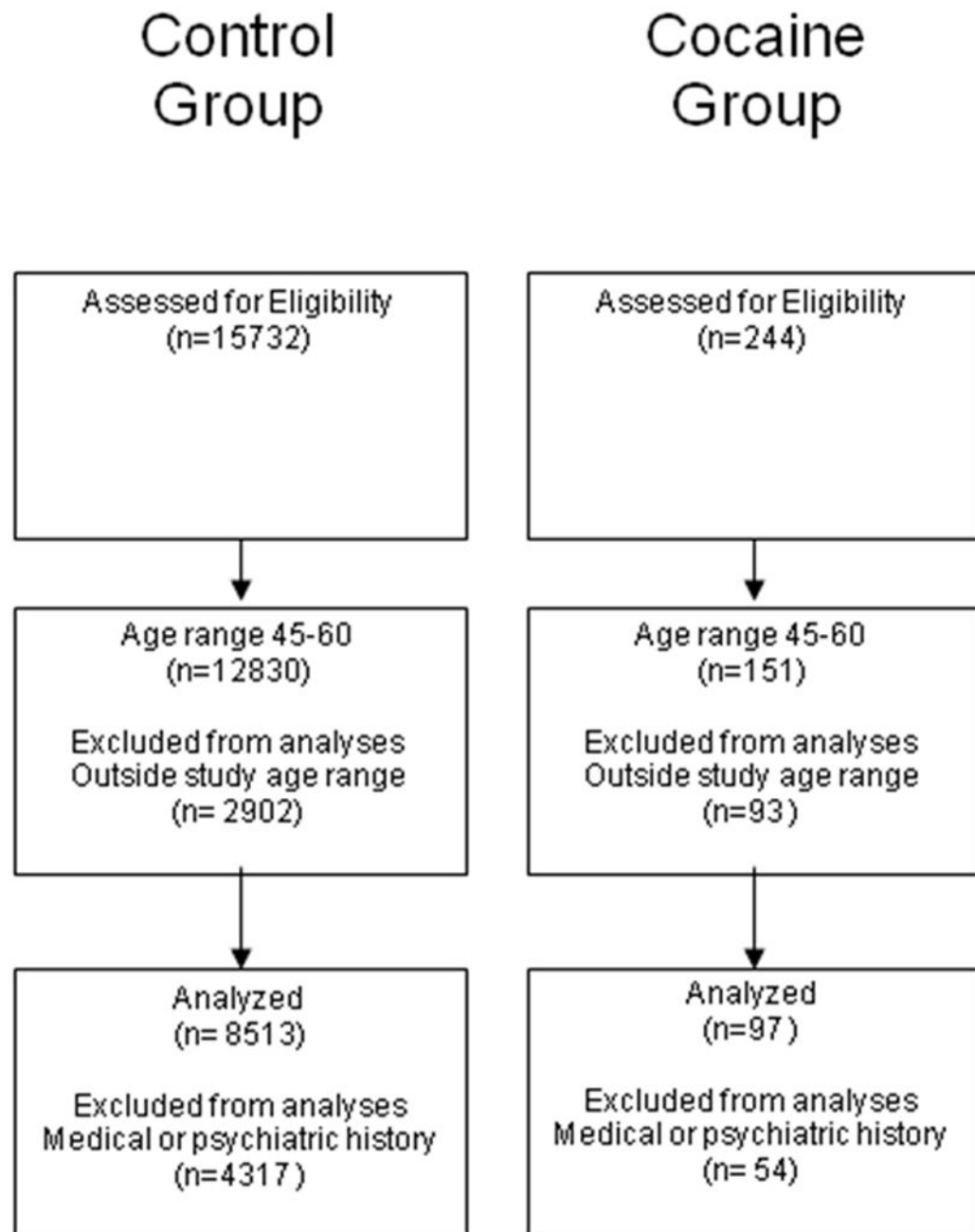


Figure 1.

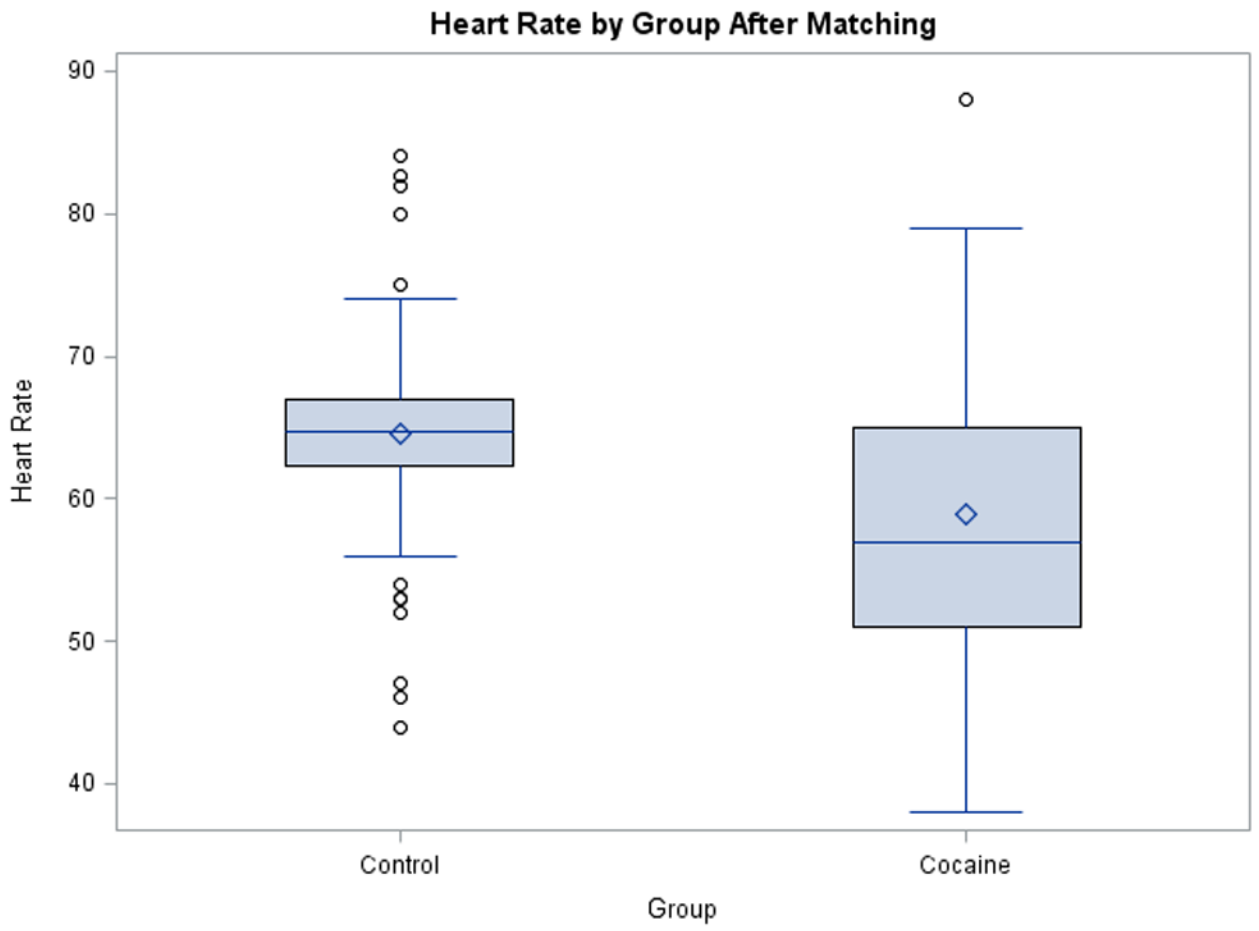


Figure 2.

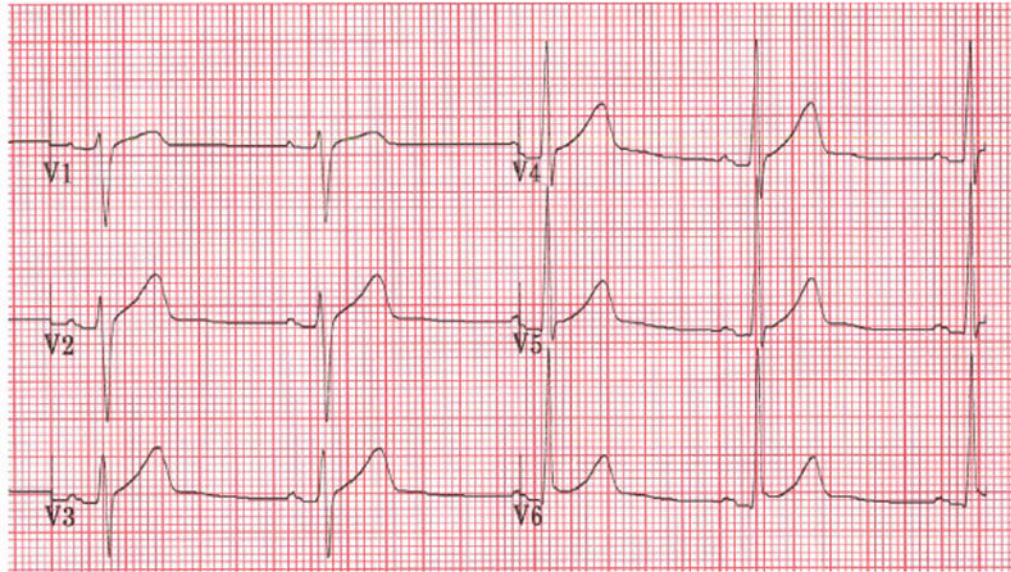


Figure 3.

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Table 1Demographic and ECG characteristics at Baseline by Group^a

	Cocaine-Dependent Subjects (n= 97)	Controls (n= 8513)	p-value
Age, mean (SD), years	49.5 (3.9)	51.8 (4.5)	< 0.0001
Male, No. (%)	83 (85.6)	3706 (45.5)	< 0.0001
Female, No. (%)	14 (14.4)	4447 (54.5)	< 0.0001
African American Race, No. (%)	73 (78.4)	1753 (21.5)	< 0.0001
ECG measured heart rate, mean (SD), bpm	58.9 (9.8)	66.2 (9.6)	< 0.0001
Bradycardia, No. (%)	58 (59.8)	1940 (23.9)	< 0.0001
Severe Bradycardia (HR < 50), No. (%)	22 (22.7)	286 (3.5)	< 0.0001
Early repolarization, No. (%)	27 (27.8)	109 (1.28)	< 0.0001
QT interval-Female, mean (SD), ms	417.3 (37.7)	--	NA
QT interval-Male, mean (SD), ms	420.5 (33.1)	--	NA
QTc interval-Female, mean (SD), ms	420.6 (16.3)	--	NA
QTc interval-Male, mean (SD), ms	409.8 (14.8)	--	NA
Left Ventricular Hypertrophy (Cornell criteria), No. (%)	1 (1.0)	76 (1.0)	0.9494
Years of Cocaine Use, mean (SD) [range]	16.5 (7.7) [<1 to 33]	NA	
Days of Cocaine Use in Last 30 days, mean (SD) [range]	16.3 (9.1) [1 to 30]	NA	

^aThese are the unweighted statistics obtained prior to matching. The analysis used the weighted statistics from the matching analysis. The weighted statistics after matching are available upon request.

Table 2

Adjusted effect size estimates for cases relative to controls

	Odds Ratio	95% LCL	95% UCL	p-value
Early	4.92	2.73	8.87	0.0001
Repolarization, adjusted for heart rate				
Early Repolarization, unadjusted for heart rate	5.58	3.13	9.94	0.0001
Bradycardia	3.02	1.95	4.66	0.0001
Severe Bradycardia	5.11	2.95	8.84	0.0001
	B weight	95% LCL	95% UCL	p-value
Heart Rate	-5.84	-7.85	-3.82	0.0001

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