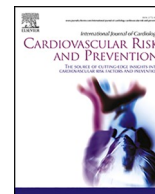




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## Effects of cocaine and/or heroin use on resting cardiovascular function

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### ABSTRACT

**Background:** Regular cocaine and/or heroin use is associated with major health risks, especially cardiovascular disease, but confounded by other factors. We examined effects of chronic (years regular use) and recent (past-month) cocaine and heroin use, controlling for other factors, on resting cardiovascular function.

**Methods:** In a sample of 292 cocaine and/or heroin users, we assessed demographics, body mass index (BMI), substance use history, electrocardiogram, heart rate (HR) and blood pressure (BP). Three-block (1: demographics, BMI; 2: tobacco, alcohol, cannabis; 3: cocaine, heroin) regression analyses were conducted to predict cardiovascular measures.

**Results:** Higher BMI predicted increased systolic and diastolic BP (as did older age), increased supine HR, and longer QRS duration, QTc interval, PR interval, and P-wave duration. Past-month cannabis-use days predicted higher systolic BP, lower supine HR, and greater likelihood of early repolarization and ST elevation; average daily cannabis use predicted shorter QTc interval. Average daily alcohol use predicted higher diastolic BP, higher supine HR and lower likelihood of sinus bradycardia (HR < 60 bpm). Past-month tobacco-use days predicted shorter QTc interval and lower lower likelihood of profound bradycardia (HR < 50 bpm). Past-month heroin-use days predicted lower seated HR, greater likelihood of sinus bradycardia and lower likelihood of left ventricular hypertrophy. More years of regular cocaine use and past-month cocaine-use days predicted longer QTc interval. **Conclusions:** Cocaine and heroin use incrementally predicted modest variance in resting bradycardia and QTc interval. Clinicians should first consider demographics and recent use of tobacco, alcohol and cannabis before assuming cocaine and heroin affect these measures.

### 1. Introduction

Widespread use of cocaine and opioids is strongly implicated in rising drug overdose deaths [1,2]. Cocaine and opioids (e.g. heroin) may be used independently, simultaneously to experience their combined effects (primarily mediated by dopamine reuptake inhibition and *mu*-opioid receptor agonism, respectively), or in temporal sequence to enhance positive effects and mitigate negative effects [3]. Concurrent use of these drugs may synergistically damage cardiovascular function [4,5]. Given high rates of cocaine and heroin use, alone and in combination [3,6], it is important for clinicians to appreciate effects of both chronic and recent use of these drugs on resting cardiovascular function.

Acute cocaine intake results in sympathomimetic effects, including increased heart rate (HR), contractility, blood pressure (BP) and

vasoconstriction. These combined effects increase demand for oxygen yet decreased supply [7] and increase risks of myocardial infarction, cardiomyopathy, arrhythmia, and other cardiovascular diseases [8]. Based on electrocardiogram (ECG) evaluation, recent cocaine use may lead to bradycardia by delaying repolarization and prolonging QTc interval [9,10]. Severity of bradycardia is associated with chronicity, but not recency, of cocaine use, and diagnosis of cocaine dependence corresponded to increased odds of early repolarization, bradycardia (<60 bpm) and profound bradycardia (<50 bpm) [11]. Another study found that two or more uses of cocaine >30 days apart predicted sinus bradycardia [12].

In contrast to cocaine, heroin acts on the vasomotor center to stimulate parasympathetic activity, thereby lowering HR and BP [4,13]. Chronic effects of heroin are less clear. Lipski et al. [14] compared

*Abbreviations list:* ECG, electrocardiogram; HR, heart rate; BP, blood pressure; BMI, body mass index; bpm, beats per minute.

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heroin-only users and methadone-maintained polydrug users; they found 19% of heroin users had QTc prolongation and 19% exhibited bradyarrhythmias whereas, in the methadone group, 34% had QTc prolongation and 32% bradyarrhythmias. Although QT/QTc prolongation is observed in some chronic heroin users, abnormal QT/QTc findings are mostly attributable to methadone (and are related to dose- and time-in-treatment) rather than heroin [15–17]. Thus, more concern has focused on methadone-related ECG abnormalities whereas effects of heroin on ECG remain understudied.

Interpretation of cocaine- or heroin-related cardiovascular sequelae is complicated by the effects of demographic factors such as race [18–20], sex [18,20–22], and age [18,23–25], and body mass index (BMI) [18,26–29] on cardiovascular function. Studies have found that race, sex, and age positively associate with BP, HR, and QTc duration whereas obesity positively associate with BP, HR, QRS complex duration, QTc, PR interval, and P-wave duration. Further, cocaine and heroin use typically co-occur with other substance use [3,30], especially tobacco, alcohol and cannabis, each of which has unique impacts on the cardiovascular system [4,31–36]. Moreover, these drugs can modulate effects of cocaine and/or heroin. For example, by attenuating vasoconstrictive effect of cocaine, cannabis-induced vasodilation enhances absorption of cocaine and its toxic effects [37]. Such findings suggest clinicians should consider demographics, BMI, and polysubstance use when examining cardiovascular effects of individual drugs.

The present study addressed these knowledge gaps by investigating the effects on baseline cardiovascular function of: (1) demographics, (2) BMI, and (3) long-term and past-month intake of commonly-used substances among a sample of primary cocaine and/or heroin users. The aim was to establish whether cocaine and/or heroin use predicted variance in cardiovascular outcomes beyond demographics, BMI, and common substance use. We hypothesized that, after covariate control, chronic and recent cocaine use would significantly predict resting bradycardia and/or longer QTc interval, whereas heroin use would not be related to resting cardiovascular measures.

## 2. Materials and methods

### 2.1. General study information

This report includes screening data from 6 clinical studies registered on [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT 00429767, 00608504, 00684840, 00946660, 01392092, and 01536925). The local Investigational Review Board approved all source studies, and certificates of confidentiality were obtained.

### 2.2. Participant sample

#### 2.2.1. Recruitment

Male and female volunteers ages 18–55 years old, regardless of race/ethnicity, were recruited from the Detroit metropolitan area using newspaper ads and word-of-mouth referral. All studies sought individuals who were not seeking treatment for their drug use to participate in clinical pharmacology studies involving primary heroin users, primary cocaine users, and concurrent cocaine/heroin users. Candidates first completed a phone screen to identify major psychiatric or medical contraindications to laboratory-based opioid and/or cocaine administration. Volunteers who were not initially excluded were invited for in-person screening. All provided informed consent before completing screening procedures and were compensated \$25 for the first in-person visit.

#### 2.2.2. Inclusion

Participants had to provide an alcohol-free breath sample (<0.02%) and obtain estimated IQ scores  $\geq 80$  on the Shipley Institute of Living Scale [38] to demonstrate ability to provide informed consent. To enable broader generalizability of study findings, participants were not

excluded from this analysis due to polysubstance use, medical conditions or psychiatric conditions (although they may have later been excluded from the laboratory studies).

### 2.3. Measures

#### 2.3.1. Substance use

Each participant provided a supervised urine sample that was tested onsite for cocaine metabolites, opioids and benzodiazepines (positive  $\geq 300$  ng/ml), amphetamines ( $\geq 1000$  ng/ml), barbiturates ( $\geq 200$  ng/ml), and cannabinoids ( $\geq 50$  ng/ml). Urinalysis results did not determine whether participants were included in the analyses.

Substance use screening included a standardized Drug History and Use Questionnaire (available on request) routinely used in our lab. This questionnaire assessed age at first use and age at onset of regular (i.e. at least once per week) use, which was used to determine chronicity of regular use (i.e. age at screening minus age at onset of regular use). The instrument also assessed recent use frequency including past-month (i.e. number of days of use in the past month), past-week (i.e. number of days of use in the past week) and average daily use (i.e. average number of uses per day in the past week) of all substances including cocaine, heroin, alcohol, tobacco, and cannabis.

#### 2.3.2. Medical/cardiovascular data

Results from 12-lead ECG (Burdick Atria 3100) were reviewed by a cardiologist who was blinded to case information except sex and age. Automated ECG measures were: supine HR, QRS duration (ms), QT and QT-corrected (QTc) interval (ms), PR interval (ms), and P-wave duration (ms). Automated ECG-based binary clinical measures (e.g. left ventricular hypertrophy, T-wave abnormality, ST elevation) were designated as exploratory. Sinus bradycardia was defined as supine HR < 60 bpm and profound bradycardia was defined as <50 bpm. HR and BP were also measured with a Welch-Allyn vital signs monitor while the participant was seated upright. Height and weight were recorded and used to compute BMI. Participants with positive medical findings from screening were notified by the research staff and instructed to consult their physician. A Medical History Questionnaire was also administered at screening; however, participants endorsed lifetime cardiovascular problems too rarely to be useful for data analysis.

### 2.4. Statistical analysis

All analyses were conducted using SPSS Version 26 (IBM Corporation, New York) and criterion to reject the null hypothesis was  $p < .05$ . All variables were assessed for missing data and outliers. Non-normal distributions (skewness, kurtosis) were corrected using  $\log_{10}$  transformations prior to outcome analyses. However, for ease of interpretation, raw values are presented in [Tables 1 and 2](#). Descriptive statistics are presented as mean (M)  $\pm$  1 standard deviation (SD). To conduct racial group comparisons, a small number of participants who did not self-identify as African American or Caucasian were excluded from all analyses.

Group differences in categorical variables were tested using chi-square analysis, whereas group differences in continuous measures were tested by Analysis of Variance (ANOVA). Relationships between demographic, BMI, substance use and cardiovascular variables were first evaluated via bivariate correlations. Pearson correlations were used for continuous variables and Kendall *tau* correlations for categorical variables. Significant zero-order correlations were used to guide variable selection for multiple regression analyses.

Forward stepwise linear regression analyses were used to assess predictors of continuous cardiovascular indices (e.g. HR, BP, QTc interval). Each regression analysis had a parallel hierarchical structure, employing 3 blocks: block 1 included demographics (race, sex, age) and continuous BMI score; block 2 included measures of chronic and past-month use of tobacco, alcohol and cannabis; and block 3 included

**Table 1**  
Demographic and substance-use measures.

	Overall N = 292	African American		Caucasian		Effect(s)	F or $\chi^2$ [2]	P
		BMI < 25 n = 94	BMI > 25 n = 83	BMI < 25 n = 71	BMI > 25 n = 44			
<b>Demographics</b>								
Sex (% male)	76%	74%	72%	77%	84%	–	–	–
Age (yrs)	42.4 (9.6)	47.0 (6.7)	45.2 (7.3)	36.5 (10.0)	37.1 (10.5)	Race	83.05	.000
Education (yrs)	12.5 (1.6)	12.3 (1.5)	12.5 (1.6)	12.2 (1.4)	13.0 (2.1)	BMI	5.88	.016
<b>Urine drug screen (% positive)</b>								
Cocaine	53%	59%	57%	49%	41%	(Race)	3.80	.051
Opioids	66%	57%	47%	93%	80%	Race, BMI	39.99 6.97	.000 .008
THC	30%	36%	24%	30%	32%	–	–	–
BZD	12%	15%	6%	15%	14%	–	–	–
<b>Tobacco use</b>								
Years regular use	16.7 (6.7)	16.6 (7.5)	18.7 (6.6)	16.9 (5.5)	15.4 (7.3)	Race * BMI	4.75	.030
Current average daily intake (# cigarettes)	12.9 (9.3)	10.1 (7.7)	10.1 (8.1)	18.8 (10.2)	14.6 (7.7)	Race, BMI, Race * BMI	39.76 3.09 3.89	.000 .049 .050
# days use past week	6.1 (2.1)	5.8 (2.4)	5.8 (2.4)	6.7 (1.2)	6.2 (2.1)	Race	6.35	.012
# days use past month	25.9 (9.1)	24.6 (10.1)	25.1 (9.8)	28.3 (6.0)	26.4 (9.4)	Race	5.12	.024
<b>Alcohol use</b>								
Years regular use	14.6 (9.7)	15.4 (10.7)	17.3 (9.5)	12.2 (8.4)	11.7 (8.6)	Race	14.43	.000
Current average daily intake (# drinks)	1.5 (2.7)	2.1 (3.6)	1.8 (2.4)	0.6 (1.4)	1.4 (2.6)	Race	8.81	.003
# days use past week	1.2 (1.9)	1.7 (2.1)	1.6 (1.9)	0.4 (0.9)	0.9 (1.8)	Race	21.00	.000
# days use past month	4.7 (7.3)	6.7 (8.7)	6.1 (8.0)	1.5 (3.5)	3.0 (5.2)	Race	23.97	.000
<b>Cannabis use</b>								
Years of regular use	12.9 (7.7)	13.0 (7.7)	13.8 (8.6)	11.6 (6.8)	12.9 (6.8)	–	–	–
Current average daily intake (# use episodes)	1.1 (2.8)	1.3 (2.7)	0.8 (1.5)	1.1 (4.3)	1.0 (1.8)	–	–	–
# days use past week	1.0 (1.9)	1.0 (1.7)	1.3 (2.1)	0.8 (1.8)	1.0 (1.7)	–	–	–
# days use past month	4.0 (7.8)	3.9 (7.4)	4.5 (8.4)	3.3 (7.7)	4.2 (7.9)	–	–	–
<b>Cocaine use</b>								
Years regular use	13.3 (10.3)	15.0 (9.8)	14.8 (9.7)	10.3 (10.3)	11.5 (11.3)	Race	10.58	.001
Current average daily intake (# use episodes)	2.6 (3.4)	2.7 (2.6)	3.3 (4.2)	1.7 (3.4)	2.0 (2.9)	Race	8.06	.005
# days use past week	2.5 (2.5)	3.2 (2.7)	2.8 (2.4)	1.8 (2.3)	1.8 (2.4)	Race	15.76	.000
# days use past month	10.4 (10.6)	12.7 (10.8)	12.0 (10.5)	7.3 (10.3)	7.8 (9.5)	Race	14.39	.000
<b>Heroin use</b>								
Years regular use	10.4 (11.4)	13.7 (13.9)	7.8 (10.4)	10.0 (9.1)	8.6 (9.0)	BMI	7.08	.008
Current average daily intake (# use episodes)	3.0 (3.4)	2.7 (3.4)	2.1 (3.1)	3.8 (2.9)	4.1 (4.2)	Race	13.99	.000
# days use past week	4.5 (3.2)	4.0 (3.2)	3.0 (3.3)	6.2 (2.0)	5.7 (2.7)	Race, BMI	46.40 4.01	.000 .046
# days use past month	15.8 (13.9)	13.1 (13.8)	9.8 (13.0)	22.3 (11.9)	22.7 (12.1)	Race	50.05	.000

Table cells present mean (SD) or percentage; Abbreviations: BMI = body mass index. THC = tetrahydrocannabinol. BZD = benzodiazepines.

measures of chronic and past-month use of heroin and cocaine. Logistic regression analyses, using the forward likelihood ratio method, were used to investigate predictors of clinically-relevant, non-rare (>10% of this sample) dichotomous cardiovascular measures: systolic BP > 140 mm Hg, diastolic BP > 90 mm Hg, sinus bradycardia, left ventricular hypertrophy, and sinus arrhythmia.

### 3. Results

#### 3.1. Participant characteristics

Table 1 presents M ± 1 SD demographic and substance use data for the sample, stratified by self-identified Race (African American vs. Caucasian) and Overweight (BMI > 25 vs. BMI < 25) group. Race and BMI groups were statistically independent,  $\chi^2 [2] = 2.11, p = .146$ . There were significant race differences across a range of variables: Relative to African Americans, Caucasians in this sample were younger, more likely to test opioid-positive (but marginally less likely to test cocaine-positive),

**Table 2**  
Cardiovascular measures.

	Overall N = 292	African American		Caucasian		Effect(s)	F or $\chi^2$ [2]	p
		BMI < 25 n = 94	BMI > 25 n = 83	BMI < 25 n = 71	BMI > 25 n = 44			
<b>Blood pressure (BP) measures</b>								
Systolic BP (mm Hg)	122.2 (14.8)	122.3 (14.2)	127.9 (15.2)	115.8 (14.0)	121.7 (12.6)	Race, BMI	13.18 10.98	.000 .001
SBP $\geq$ 140 mm Hg (%)	12%	12%	20%	7%	7%	Race	4.99	.025
Diastolic BP (mm Hg)	77.5 (11.3)	78.2 (10.9)	81.7 (11.8)	72.8 (10.9)	75.8 (8.9)	Race, BMI	18.29 6.05	.000 .015
DBP $\geq$ 90 mm Hg (%)	15%	15%	25%	10%	5%	Race	7.67	.006
<b>Heart rate (HR) measures</b>								
Seated HR (bpm)	72.2 (11.6)	72.1 (11.2)	71.3 (11.1)	71.6 (12.4)	74.7 (12.0)	–	–	–
Supine HR (bpm)	64.5 (10.6)	63.5 (9.3)	64.6 (10.8)	63.7 (10.9)	67.6 (11.9)	(BMI)	3.78	.053
% Sinus bradycardia (<60 bpm)	37%	33%	41%	42%	32%	–	–	–
% Profound bradycardia (<50 bpm)	5%	4%	6%	6%	5%	–	–	–
<b>ECG measures (ms)</b>								
QRS	86.4 (9.8)	83.7 (8.1)	84.7 (8.0)	88.6 (12.4)	91.5 (9.2)	Race	25.55	.000
QT interval	404.2 (36.7)	404.5 (34.7)	406.6 (35.2)	404.0 (39.1)	399.2 (40.1)	–	–	–
QTc interval	413.9 (15.1)	411.9 (14.6)	416.9 (16.2)	410.7 (14.7)	417.9 (13.1)	BMI	11.26	.001
PR interval	154.4 (24.3)	151.6 (27.2)	160.8 (23.7)	150.8 (20.7)	154.0 (23.0)	BMI	4.42	.036
P-wave duration	103.0 (11.0)	103.7 (11.0)	104.9 (11.5)	99.6 (10.0)	103.8 (10.9)	Race, BMI	3.90 4.24	.049 .040
<b>Exploratory ECG measures (% positive)</b>								
Left ventricular hypertrophy	15.1%	23.4%	15.7%	8.5%	6.8%	Race	7.82	.005
Sinus arrhythmia	11.0%	6.4%	8.4%	19.7%	11.4%	Race	5.96	.015
Atrial enlargement	6.9%	6.4%	9.6%	5.6%	4.6%	–	–	–
T-wave abnormality	5.1%	5.3%	12.1%	0.0%	0.0%	Race	10.30	.001
Early repolarization	4.1%	5.3%	6.0%	2.8%	0.0%	–	–	–
ST elevation	1.7%	3.2%	2.4%	0.0%	0.0%	–	–	–

Table cells present mean (SD) or percentage.

Abbreviations: BMI = body mass index. BP = blood pressure. bpm = beats per minute. DBP = diastolic blood pressure. ECG = electrocardiogram. HR = heart rate. mm Hg = millimeters mercury. PR = PR interval of ECG waveform. QRS = QRS segment of ECG waveform. QT(c) = QT or QTc (normalized) segment of ECG waveform. SBP = systolic blood pressure. ST = ST segment of ECG waveform.

and reported heavier and more frequent use of tobacco and heroin; whereas Caucasians reported shorter lifetime duration and less past-month use of alcohol and cocaine. Relative to normal-weight participants (BMI < 25), overweight participants reported more years of education, were less likely to test opioid-positive, and endorsed fewer years of regular heroin use and fewer days of past-week heroin use.

### 3.2. Resting cardiovascular function

Table 2 presents M  $\pm$  1 SD descriptive data in the overall sample, again stratified by race and BMI groups – as these were important control variables. African American race was associated with significantly higher resting systolic and diastolic blood pressures (and for a higher percentage meeting clinical cutoffs for elevated BP), shorter QRS duration, and longer P-wave duration. A significantly higher percentage of African Americans (compared to Caucasians) met ECG criteria for left ventricular hypertrophy and T-wave abnormality, and a lower percentage met criteria for sinus arrhythmia. Being overweight was associated with significantly higher systolic and diastolic BP, longer QTc and PR intervals and P-wave duration. Biological sex of participants influenced two ECG measures: males had longer QRS durations and longer QTc intervals than females.

Table 3 shows significant predictors of resting cardiovascular measures based on blocked regression analyses. Generally speaking, different combinations of predictors explained modest degrees of variance in cardiovascular outcomes: 11–15% total variance in systolic blood pressure, QRS duration, and QTc interval; 4–10% total variance in supine HR and bradycardia measures, QT interval, P-wave duration, and likelihood of sinus arrhythmia, and left ventricular hypertrophy; and 2%

variance in seated HR and PR interval.

Adjusting for covariates, higher BMI positively predicted systolic and diastolic BP, increased supine HR, and longer QRS duration, QTc interval, PR interval, and P-wave duration. Older age was also associated with higher systolic and diastolic BP. Race remained related to several ECG indices in adjusted analyses (QRS and P-wave duration, and likelihood of sinus arrhythmia and left ventricular hypertrophy).

Adjusting for covariates, measures of past-month frequency and amount of substance use had more reliable effects than chronicity (lifetime duration of regular use) on cardiovascular measures. Past-month number of days of cannabis use positively predicted higher systolic BP and lower supine HR, whereas average daily cannabis use predicted shorter QTc interval. Longer duration of regular cannabis use contributed to greater likelihood of sinus bradycardia. Average daily alcohol use predicted higher diastolic BP, higher supine HR, shorter QT interval, and lower odds of sinus bradycardia (HR < 60 bpm). Past-month number of days of tobacco use predicted shorter QTc interval.

Adjusting for covariates, past-month number of days of heroin use predicted lower seated (but not supine) HR, higher likelihood of sinus bradycardia, and lower likelihood of left ventricular hypertrophy. Longer lifetime duration of regular cocaine use and more past-month days of cocaine use predicted longer QTc interval; adjusting for covariates, cocaine use measures were not associated with any other cardiovascular indices.

## 4. Discussion

The present study examined whether chronic or recent use of cocaine or heroin would be associated with resting cardiovascular measures,

**Table 3**  
Predictors (blocked regression) of cardiovascular measures in overall sample (N = 280).

Dependent measure	Significant predictors	Standardized beta value (odds ratio)	Cumulative adjusted r [2] or Nagelkerke r [2]	t or Wald (p)
Blood pressure				
	Systolic BP (mm Hg) <i>F</i> (3,275) = 15.24, <i>p</i> < .000	BMI ¶ .243 Age ¶ .269 Cannabis days past mo. (log <sub>10</sub> ) .117	.063 .123 .133	4.33 (.000) 4.76 (.000) 2.06 (.040)
	Diastolic BP (mm Hg) <i>F</i> (3,275) = 17.13, <i>p</i> < .000	Age ¶ .292 BMI .207 Avg. daily alcohol use (log <sub>10</sub> ) .127	.091 .135 .148	5.26 (.000) 3.72 (.000) 2.28 (.023)
Heart rate				
	Seated HR (bpm) <i>F</i> (1,278) = 6.15, <i>p</i> = .014	Heroin days past mo. -.147	.018	-2.48 (.014)
Supine HR (bpm) <i>F</i> (4,275) = 7.70, <i>p</i> = .000	BMI .110	.013	1.91 (.057)	
	Avg. daily alcohol use (log <sub>10</sub> ) -.201	.075	4.39 (.000)	
	Years regular alcohol use -.131	.088	-3.36 (.001)	
	Cannabis days past mo. (log <sub>10</sub> )		-2.20 (.027)	
Sinus bradycardia (%) (<60 bpm)	Avg. daily alcohol use (log <sub>10</sub> ) -1.021	1.024	10.42 (.001)	
	Years regular cannabis use		5.80 (.016)	
	Heroin days past mo.		4.24 (.040)	
	Tobacco days past mo. (log <sub>10</sub> )		5.72 (.017)	
ECG				
	QRS duration (ms) <i>F</i> (3,276) = 12.56, <i>p</i> < .000	Race (whites longer QRS) .274 Sex (males longer QRS) .133 BMI .171	.069 .111 .096	4.80 (.000) 3.02 (.003) 2.34 (.020)
	QT interval (ms) <i>F</i> (2,277) = 6.43, <i>p</i> < .002	Avg. daily alcohol use (log <sub>10</sub> ) -.204 Tobacco days past mo. (log <sub>10</sub> ) .145	.022 .041	-3.30 (.001) 2.36 (.019)
	QTc interval (ms) <i>F</i> (6,273) = 7.77, <i>p</i> < .000	BMI .225 Sex (males shorter QTc) -.152 Avg. daily cannabis use (log <sub>10</sub> ) .421 Tobacco days past mo. (log <sub>10</sub> ) .122 Cocaine days past mo. .268 Years regular cocaine use .200	.046 .072 .089 .117 .127 2.68 (.008) 2.00 (.047)	3.99 (.000) -2.79 (.006) -2.66 (.008) -1.92 (.056) 2.68 (.008) 2.00 (.047)
PR interval (ms) <i>F</i> (1,278) = 7.75, <i>p</i> = .006	BMI .165	.024	2.78 (.006)	
P-wave duration (ms) <i>F</i> (2,277)	BMI .178 Race (whites) -.118	.037 .044	3.03 (.003)	

**Table 3 (continued)**

Dependent measure	Significant predictors	Standardized beta value (odds ratio)	Cumulative adjusted r [2] or Nagelkerke r [2]	t or Wald (p)
Sinus arrhythmia (%)	shorter P-wave) Race (whites more SA)	.404	.040	-2.00 (.047) 5.61 (.018)
	Left ventricular hypertrophy (%)	Race (whites more LVH) -.969 Heroin days past mo.	2.344 -969	.091 3.77 (.052) 5.09 (.024)

\* Each table entry indicates a predictor variable that was significantly associated with the outcome (left column; omnibus model statistics shown) in regression analysis. N.S. indicates no significant findings. F = females, M = males, B = black, W = white, and BMI = body mass index.

¶ Indicates predictor also significant for clinical threshold (Systolic BP ≥ 140, Diastolic BP ≥ 90).

after controlling for other clinically relevant factors known to affect these outcomes including demographics, BMI, and other commonly used substances. Previous studies have mostly focused on specific effects such as cocaine use, without adequate control for these various influential factors.

Controlling for demographic and substance use variables, we found that neither chronic nor past 30-day use of heroin or cocaine predicted resting systolic or diastolic BP. Although cocaine use acutely increases BP due to increased catecholamine levels systemically [39], our study focused on less immediate cocaine use. Kozor et al. [40] found that self-reported cocaine use (at least monthly during the past year) was linked to high systolic BP compared to those who denied prior cocaine exposure; although sample size was relatively small, the investigators controlled for several demographic and substance use factors.

Higher BMI and older age predicted elevated systolic and diastolic BP, together accounting for 12–14% of variance in these outcomes. These results are consistent with prior studies showing effects of age [24, 41] and BMI [42,43] on blood pressure. In addition, more-frequent past-month cannabis use predicted higher systolic BP, and higher past-month average daily alcohol use predicted elevated diastolic BP, but in each case the incremental variance explained was minimal (<2%). Similar modest associations have been reported for cannabis use and systolic BP [44] and for alcohol use and diastolic BP [45,46].

To control for possible effects on HR we measured resting HR in two different positions, seated and supine. The latter was obtained at the same time as ECG indices, and may enhance detection of bradycardia due to less sympathetic drive. For seated HR, more past-month heroin use days was significantly related to bradycardia. For the supine measure, higher BMI and average daily alcohol use were related to higher HR, whereas longer duration of regular alcohol use and more days of past-month cannabis use were associated with lower HR; together, these four predictors accounted for 8.8% of the variance in supine HR.

We also classified participants with supine HR < 60 bpm as having sinus bradycardia and those with supine HR < 50 bpm as having profound bradycardia. Overall, 37% of participants had sinus bradycardia while only 5% had profound bradycardia. Presence of sinus bradycardia was predicted by less daily alcohol use, more years regular cannabis use, and more past-month heroin use days; together, these three factors explained 10.7% of the variance in this categorical measure. The association of past-month heroin use and bradycardia mirrors bradycardia that can occur during acute heroin intake, including increased parasympathetic activity, decreased sympathetic activity and stimulation of mast cells to release histamine [4]. It is unclear whether chronic heroin intake produces adaptations in these or other neural mechanisms that would promote bradycardia. Our finding that chronic cannabis use is related to resting bradycardia is consistent with extant research [47].



Few studies have addressed the relationships of regular alcohol or nicotine use to resting bradycardia; thus, the significance of these factors predicting sinus and profound bradycardia, respectively, is unclear.

Contrary to hypothesis, we did not find a significant effect of chronic cocaine use on resting HR (but see discussion of QTc interval, below). One impetus for our study was to replicate findings [11,12] that chronic cocaine use is related to increased odds of bradycardia. While both studies excluded subjects with history of illicit drug use or medical illness (and prescription drugs), Sharma et al. [11] did not exclude cocaine users with histories of concurrent cannabis or alcohol use, making it difficult to rule out these factors as it relates to our findings. Further investigation with larger sample sizes and careful controls are needed to determine whether this association is reliable.

Increased cocaine-use frequency during the past month and cocaine-use chronicity (years of regular use) both significantly predicted longer QTc intervals; yet, these two factors explained only 2.3% of the variance, after controlling for effects of other predictors (higher BMI, male sex, less past-month cannabis and tobacco use) that explained 10.4% of the variance. Cocaine use has previously been linked to QTc lengthening, due to its blockade of potassium channels [48,49]. As QTc interval adjusts for HR, this electrophysiological index could be a more sensitive biomarker of drug effects than either resting HR or QT interval (the latter was predicted by past-month average alcohol use and tobacco-use days). These modest findings for cocaine use suggest that clinicians should attend to multiple determinants of QTc interval in addition to cocaine, given prior research showing strong associations of QTc interval with BMI [50] and sex [20].

Neither cocaine nor heroin predicted QRS duration, PR interval, P-wave duration (all positively related to higher BMI), nor odds of early repolarization or ST elevation (both positively associated with past-month cannabis-use days). However, more past-month heroin-use days was significantly related to lower seated (but not supine) HR, increased likelihood of sinus bradycardia, and reduced likelihood of left ventricular hypertrophy. One potential explanation for this pattern is that chronic opioid stimulation could enhance parasympathetic stimulation and, thus, provide a protective effect.

In the present study, we predicated our analyses on the assumption that polysubstance use is the norm, not the exception, and with an eye toward generalizability and clinical application. Our findings support the idea that this complex profile of drug use needs to be considered during clinical assessment. While evaluating individuals who present with chronic use of heroin and/or cocaine, it is important to recognize that cannabis, tobacco, and alcohol may also exert significant effects on cardiovascular function, and that use of these common substances could overshadow the effect of illegal drugs on cardiovascular outcomes.

#### 4.1. Study limitations

The present study has several limitations. First, it lacks a non-drug control group; thus, comparisons to the general population cannot be made. Second, demographic generalizability of our findings is limited, considering our sample was predominantly male and limited to one geographic site with over-representation of African Americans. Third, drug-use history was self-reported and may be biased. Fourth, psychiatric history was not used to exclude participants; therefore, conditions such as anxiety or depression may have contributed to outcomes. However, we believe retaining these factors helps broaden the generalizability of findings to and relevance to clinical decision making. Fifth, drug purity of cocaine or heroin was unstandardized due to varying sources of these drugs. Confounding ingredients or substances could impact our study's findings.

#### 5. Conclusions

Cardiovascular disease has been increasingly linked to regular use of substances such as cocaine and heroin. We examined effects of using

cocaine, heroin and other substances (tobacco, alcohol, cannabis), as well as other demographic factors (BMI, race, sex), on predicting resting cardiovascular measures. After accounting for covariates (as a clinician would conservatively do), cocaine and heroin explained only modest incremental variance in resting bradycardia and QTc interval. Clinicians should first consider effects of demographics (especially race and BMI) and recent use of tobacco, alcohol and cannabis before assuming that cocaine and heroin are influencing these measures.

#### Author contributions

Mark Greenwald: Funding acquisition, conceptualization, data curation, formal analysis, supervision, writing original draft and editing. Leslie Lundahl: Conceptualization, Investigation, editing. Lina Shkokani: Literature review, initial data curation and analysis, drafting. Shabber Syed: Literature review, drafting. Renato Roxas: Investigation (read ECGs), reviewing. Phillip Levy: Conceptualization, editing.

#### Declaration of competing interest

None.

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