Published in final edited form as:

Am J Drug Alcohol Abuse. 2008 ; 34(4): 489–498. doi:10.1080/00952990802082214.

Exercise Stress Testing in Recently Abstinent Chronic Cocaine Abusers

Praveen Kanneganti, B.A.¹, Richard A. Nelson, M.D.¹, Susan J. Boyd, M.D.^{1,*}, Roy C. Ziegelstein, M.D.², and David A. Gorelick, MD, Ph.D.¹

¹ Office of the Science Director, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Department of Health and Human Services, Baltimore, Maryland, USA

² Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Abstract

We compared treadmill exercise stress testing (EST) in 28 medically screened, chronic cocaine users with the cardiovascular effects of an IV cocaine challenge (25 mg or 50 mg). All subjects had a clinically normal EST and echocardiography (except 2 subjects had septal wall hypokinesis). The EST produced significantly greater increases in heart rate and rate-pressure product than did the cocaine challenges. These findings suggest that EST may not provide additional diagnostic information in medically screened cocaine users. EST may cause more cardiac work (indicated by heart rate and blood pressure) than intravenous cocaine (at the doses in this study).

Keywords

Abstinent; cocaine; exercise stress test; echocardiography

INTRODUCTION

Cocaine had an estimated 2.4 million current users in the United States during 2006 (1). Cocaine use has major adverse effects on the cardiovascular system, including tachycardia, arrhythmias, elevated blood pressure, and myocardial infarction (2,3). These effects result in complaints of chest pain, palpitations, and shortness of breath by cocaine-using patients presenting to emergency departments (4).

The acute cardiovascular effects of cocaine, such as dose-dependent increases in heart rate, blood pressure, and vascular resistance, and decreased blood flow in several vascular beds, have been demonstrated in human laboratory studies (5–7). Less well studied are the cardiovascular sequelae of chronic cocaine use outside the context of immediate cocaine use.

Exercise stress testing (EST) is a clinically validated, non-invasive method for evaluating coronary artery disease and working capacity (8). We are aware of four studies that used EST in recently abstinent cocaine users, two using a treadmill (Bruce protocol) and 2 using a bicycle. In one study, 16 chronic cocaine abusers with left-ventricular hypertrophy (LVH) (by echocardiography) showed an exaggerated pressor response to treadmill exercise (mean [$\pm$ SD] 14.2 ± 15.3 days after last cocaine use), while 33 chronic abusers without LVH did not (12.8

Address corresponding author to David A. Gorelick, NIDA IRP, 251 Bayview Boulevard, Baltimore, MD 21224–2816. E-mail: dgorelic@intra.nida.nih.gov.

*Currently at Department of Psychiatry, University of Maryland School of Medicine, Baltimore, Maryland, USA.

± 11.6 days after last cocaine use) (9). A second study found that of 20 male chronic cocaine users undergoing an exercise treadmill testing a mean of nine days after their last cocaine use, only one had electrocardiographic evidence of ischemia (10). In a third study, 35 chronic cocaine smokers had reduced aerobic capacity and maximal heart rates during cycle ergometry (a minimum of 12 hours after last cocaine use) compared to 29 age-matched healthy controls (11). In the fourth study, 15 asymptomatic cocaine and alcohol abusers similarly had a lower mean heart rate at every point during bicycle exercise (5.4 days [range 2–14 days] after last cocaine use) than 10 age-matched healthy controls (12).

To our knowledge, there have been no studies comparing the cardiovascular effects of EST to those elicited by cocaine administration in the same group of cocaine users. This study evaluated the cardiovascular effects of EST among otherwise healthy cocaine users and compared them to those of cocaine administration within the same subjects.

METHODS

Design

This study is a retrospective secondary analysis of cardiovascular data from a double-blind, within-subject study that investigated the effects of intravenous (IV) infusion rate and dose on responses to cocaine (13). The study was approved by the NIDA Institutional Review Board.

Subjects

Non-treatment-seeking, adult (21–40 years old) cocaine users were recruited from the community. Eligibility criteria included a history of intravenous and/or smoked cocaine use for at least one year with use during the month prior to study entry, good current physical and psychological health, no personal history of cardiovascular disease or adverse cardiovascular effects from cocaine use, and no history of cardiovascular disease or sudden death before age 50 in first-degree relatives. Current health was assessed with a comprehensive medical and psychological evaluation, including medical history, physical examination, laboratory tests, 12-lead electrocardiogram (ECG) with three-minute rhythm strip, echocardiogram, and treadmill exercise-stress test using the Bruce protocol (8). Subjects gave written informed consent and were paid for their participation.

Procedure

Subjects resided on the closed residential research unit at NIDA IRP for up to five weeks. The EST was administered 1–32 days (mean = 6.2, S.D. = 6.6) after admission. Each subject who qualified for cocaine administration was scheduled to receive double-blind each of three IV cocaine doses (10 mg, 25 mg, 50 mg) in ascending order at each of three infusion durations (10 seconds, 30 seconds, and 60 seconds), plus a placebo (normal saline) infusion, in separate experimental sessions at least 48 hours apart. Thus, each subject was scheduled to receive 10 sessions (9 sessions of cocaine administration). Sessions involving administration of 25 mg (9 subjects) and 50 mg (6 subjects) over 10 seconds were used for this secondary analysis because they are closest to the larger doses and quicker injection times used by IV cocaine users in the community (14,15). Non-invasive monitoring of heart rate and blood pressure by standard clinical methods was done for one hour after each cocaine administration.

Data Analysis

Characteristics of different subject groups were compared using Student's *t*-tests for continuous variables and Fisher's exact tests for categorical variables. Within-subject comparisons of stress test and cocaine administration responses were analyzed using matched

pair *t*-tests. The two-tailed significance level was $p < .05$. Statistical analyses were performed with Microsoft Excel 2003 (Microsoft, Redmond, Washington).

RESULTS

Forty-three subjects (age range 22–40 years) consented to the primary study (see Table 1 for subject characteristics). Twenty-eight subjects had an EST and provided data for this secondary analysis. Nine subjects received a 25 mg IV cocaine challenge; six also received a 50 mg IV cocaine challenge. These nine subjects provided data to compare with EST. Subjects who received a cocaine challenge of 25 mg or 50 mg did not differ significantly in demographic or substance use characteristics from subjects who did not receive a cocaine challenge or received a cocaine challenge of 10 mg (Table 1).

All 28 subjects had a clinically normal EST (Table 2). Twenty-seven subjects reached their predicted heart rate (85% of [220-age]). One subject had the test stopped prematurely because of fatigue. Only 1 subject reached a peak systolic blood pressure above 210 mm Hg, considered an exaggerated pressor response to exercise.

Twenty-seven subjects underwent echocardiography at rest. Twenty-five subjects had a normal echocardiogram. Two subjects had septal wall hypokinesis with mild left ventricular dysfunction. No subject had left ventricular hypertrophy (LVH).

EST produced significantly greater increases in heart rate ($p = 2.66 \times 10^{-6}$), systolic blood pressure ($p = .03$), and rate-pressure product ($p = 3.3 \times 10^{-5}$) than did the 25 mg IV cocaine challenge, and significantly greater increases in heart rate ($p = .001$) and rate-pressure product ($p = .002$) than did the 50 mg IV cocaine challenge (Table 3). The time to reach peak heart rate was 5.5 minutes longer during the stress test than during cocaine infusion at 25 mg ($p = .02$), and 1.4 minutes longer than during cocaine infusion at 50 mg ($p = .48$) (Table 3).

DISCUSSION

All 28 subjects in the current study had a clinically normal treadmill EST. This is consistent with results in 119 recently abstinent, medically screened cocaine abusers (15 also abusing alcohol) from four published studies (9–12), only 1 of whom had electrocardiographic evidence suggesting myocardial ischemia(10). Two subjects in the current study had mild left ventricular dysfunction on echocardiography, which did not affect their normal EST results. These findings suggest that EST may not add any additional cardiac diagnostic information in asymptomatic, recently abstinent chronic cocaine abusers who have already been evaluated as normal on the basis of medical history, physical examination, routine blood tests, and 12-lead ECG with 3-minute rhythm strip.

Only 1 of 28 subjects experienced a peak systolic blood pressure above 210 mmHg, indicating that an exaggerated pressor response to maximal exercise was not present in this group of chronic cocaine users. This is consistent with the four prior studies, which found an exaggerated pressor response to exercise only in cocaine users with LVH detected on echocardiography (9–12).

Two prior studies found a decreased heart rate response to bicycle exercise among cocaine abusers (30% were also alcohol abusers) compared to age-matched healthy controls (11,12). The current study did not find a decreased heart rate response to treadmill exercise in 28 cocaine abusers. The 50 subjects from those published studies had a mean [SD] age of 38.4 [4.1] years, were 72% male, and had .5–19 years of frequent cocaine use. Subjects in this study included a larger percentage of males (93%), but had a similar duration of cocaine use (range 2–24 years) and were within 4 years in mean age (Table 1). Therefore, the difference in findings is unlikely

to be due to differences in subject characteristics, but may be due to the difference in exercise method (bicycle vs. treadmill).

To the best of our knowledge, the current study is the first to directly compare the cardiac response to EST with the response to an IV cocaine challenge in the same subjects. The standard Bruce protocol treadmill test produced significantly greater increases in heart rate, systolic blood pressure, and rate-pressure product than did a 25 mg or 50 mg IV cocaine challenge. Thus, in a sample of medically screened, physically healthy, asymptomatic, recently abstinent cocaine users, EST may result in more cardiac work (at least as indicated by heart rate and blood pressure) than a 25 mg or 50 mg intravenous dose of cocaine. This comparison may be limited in that EST results in coronary artery vasodilation and increased blood flow, while cocaine use results in coronary artery vasoconstriction and decreased blood flow (5–7). Therefore, comparing cardiovascular responses to EST to cocaine responses should be done cautiously. However, this comparison has implications for screening of research subjects and the safe conduct of human experimental studies involving cocaine administration. The response to EST may provide an indication of how research subjects may tolerate a cocaine challenge (at least at the doses used in this study).

It is unlikely that use of other substances influenced these findings. All subjects were primarily cocaine users. While many subjects also used other substances (heroin, cannabis, alcohol) (Table 1), heroin and cannabis use have not been associated with structural or electrophysiological cardiac abnormalities (16). Alcohol use has been associated with such cardiac effects, but all subjects in this study had normal 12-lead ECGs and echocardiograms with normal ejection fraction and left ventricular function.

The acute effect of cocaine or other substances is unlikely to have influenced these findings. EST was done at least 1 day after admission (mean = 6.2 days) to the closed research ward, adequate time for clearance from the blood of any recently ingested substance except cannabis. During this interval, subjects had no access to alcohol or illegal drugs. There was no significant correlation between the admission-EST interval and any cardiovascular measure (data not shown), suggesting that any cocaine use just prior to admission had no influence on the results.

This study has several limitations that affect its external validity. The IV cocaine challenge used single doses of 25 mg and 50 mg, probably lower than doses typically used in the community (14,15). However, the 50 mg dose should have produced plasma cocaine concentrations of at least 400 ng/ml (17), comparable to postmortem concentrations found during autopsies of cocaine users (18). Larger cocaine doses would likely produce more substantial increases in heart rate and systolic blood pressure, resulting in smaller differences from stress test responses. In addition, cocaine users in the community often take multiple doses of cocaine in one session, presumably resulting in even greater cardiac effects (19). Another limitation is that subjects were predominantly African-American men in their 30s, not representative of the entire population of United States cocaine users (1). Finally, the small sample size (9 subjects) used for the comparison between exercise stress testing and the cocaine challenge could have skewed the results. However, this subgroup did not differ significantly in demographic and substance use characteristics from the 19 subjects who had EST without a cocaine challenge or with a 10 mg challenge (Table 1).

CONCLUSIONS

In conclusion, this study found that medically screened, asymptomatic, recently abstinent cocaine abusers have normal responses to standard Bruce protocol treadmill EST and that their heart rate and systolic blood pressure responses to EST are significantly greater than their response to a 25 or 50 mg IV cocaine challenge. These findings suggest that single low doses

of cocaine may not exert substantial cardiac work (as indicated by heart rate and blood pressure) in carefully screened, otherwise healthy cocaine users.

Acknowledgements

Supported by the Intramural Research Program, NIH, National Institute on Drug Abuse.

References

1. Office of Applied Studies. National Survey on Drug Use and Health: National Results. Rockville, Md.: Substance Abuse and Mental Health Services Administration, September 2007; 2006. (DHHS Publication No. (SMA) 07-4293)
2. Lange RA, Hillis LD. Cardiovascular complications of cocaine use. *N Engl J Med* 2001;345:351–358. [PubMed: 11484693]
3. Mouhaffel AH, Madu EC, Satmary WA, et al. Cardiovascular complications of cocaine. *Chest* 1995;107:1426–1434. [PubMed: 7750342]
4. Brody SL, Slovis CM, Wrenn KD. Cocaine-related medical problems: Consecutive series of 233 patients. *Am J Med* 1990;88:325–331. [PubMed: 2327419]
5. Eged M, Davis GK. Cocaine and the heart. *Postgrad Med J* 2005;81:568–571. [PubMed: 16143686]
6. Levis JT, Garmel GM. Cocaine-associated chest pain. *Emerg Med Clin North Am* 2005;23:1083–1103. [PubMed: 16199339]
7. Pozner CN, Levine M, Zane R. The cardiovascular effects of cocaine. *J Emerg Med* 2005;29:173–178. [PubMed: 16029829]
8. Bruce RA, Blackmon JR, Jones JW, et al. Exercising testing in adult normal subjects and cardiac patients. *Pediatrics* 1963;32:742–756. [PubMed: 14070531]
9. Cigarroa CG, Boehrer JD, Brickner ME, et al. Exaggerated pressor response to treadmill exercise in chronic cocaine abusers with left ventricular hypertrophy. *Circulation* 1992;86:226–231. [PubMed: 1535569]
10. Nademanee K, Gorelick DA, Josephson MA, et al. Myocardial ischemia during cocaine withdrawal. *Ann Intern Med* 1989;111:876–880. [PubMed: 2817640]
11. Marques-Magallanes JA, Koyal SN, Cooper CB, et al. Impact of habitual cocaine smoking on the physiologic response to maximum exercise. *Chest* 1997;112:1008–1016. [PubMed: 9377910]
12. Moskowitz RM, Errichetti AJ. Cardiovascular evaluation after withdrawal from chronic alcohol or cocaine-alcohol abuse. *J Addict Dis* 1991;10:47–65. [PubMed: 1777499]
13. Nelson RA, Boyd SJ, Ziegelstein RC, et al. Effect of rate of administration on subjective and physiological effects of intravenous cocaine in humans. *Drug Alcohol Depend* 2006;82:19–24. [PubMed: 16144747]
14. Karch SB. Introduction to the forensic pathology of cocaine. *Am J Forensic Med Pathol* 1991;12:126–131. [PubMed: 1812853]
15. Finkle BS, McCloskey KL. The forensic toxicology of cocaine (1971–1976). *J Forensic Sci* 1978;23:173–189. [PubMed: 744960]
16. Frishman WH, Del Vecchio A, Sanal S, et al. Cardiovascular manifestations of substance abuse. Part 2: Alcohol, amphetamines, heroin, cannabis, and caffeine. *Heart Dis* 2003;5:253–271. [PubMed: 12877759]
17. Eisenberg MJ, Mendelson J, Evans GT, et al. Left ventricular function immediately after intravenous cocaine: A quantitative two-dimensional echocardiographic study. *J Am Coll Cardiol* 1993;22:1581–1586. [PubMed: 8227824]
18. Karch SB, Stephens B, Ho CH. Relating cocaine blood concentration to toxicity: An autopsy study of 99 cases. *J Forensic Sci* 1998;43:41–45. [PubMed: 9456523]
19. Karch, SB. Pathology of drug abuse. 3. New York: CRC Press; 2002.

Table 1
Demographic and substance use characteristics of 28 chronic cocaine users

Subject Characteristic	All Subjects	Not receiving cocaine challenge/Receiving 10 mg IV cocaine challenge	Receiving 25, 50 mg IV cocaine challenge	p for group difference
Number of subjects	28	19	9	
Age (years)	34.9 (4.7)	34.9 (5.0)	34.9 (4.0)	.98
Sex (n)				.55
Male	26	17	9	
Female	2	2	0	
Race (n)				.69
African-American	20	13	7	
White	8	6	2	
Weight (lbs)	178.0 (30.7)	180.0 (34.0)	178.0 (28.0)	.98
Height (inches)	69.1 (3.3)	68.6 (3.5)	70.2 (2.7)	.24
Body Mass Index (BMI)	26.2 (4.4)	26.9 (4.8)	24.8 (3.3)	.27
Cocaine Use				
Years of use	11.9 (5.8)	11.7 (5.4)	12.3 (6.8)	.8
Use in month prior to screening (days)	19.1 (6.1)	19.0 (6.5)	19.3 (5.7)	.9
Dependent (n)	6	3	3	.35
Alcohol Use (n)				
Years of use	28	19	7	
Use in prior month (days)	16.9 (6.9)	16.5 (7.0)	17.9 (7.1)	.62
Use to intoxication in prior month (days)	9.7 (6.2)	9.7 (6.3)	9.8 (6.3)	.97
Dependent (n) *	4.7 (5.8)	4.0 (6.0)	6.0 (5.6)	.42
Cigarette use (n) *	6	5	1	.63
Years of use	22	16	6	
Cigarettes per day	13.6 (5.4)	14.2 (5.2)	12.7 (5.5)	.54
Nicotine dependent	16.6 (10.4)	15.9 (10.7)	18.9 (10.1)	.54
Cannabis use (n)	7	4	3	.65
Years of use	27	19	8	
Use in prior month (days)	12.9 (7.5)	13.9 (8.2)	10.9 (6.0)	.33
Dependent (n)	3.6 (6.5)	2.2 (3.4)	6.4 (10.2)	.11
Heroin use (n)	1	1	0	1.00
Years of use	24	18	6	
Use in prior month (days)	10.1 (7.5)	11.6 (6.9)	6.9 (8.1)	.12
	6.9 (5.9)	8.1 (5.8)	4.4 (5.6)	.13

Data presented as mean (standard deviation) or number of subjects (n).

Substance dependence based on DSM-IV criteria.

* Due to missing data, 24, 17, and 7 subjects, respectively, provided data for cigarette use.

Table 2

Cardiovascular response to treadmill exercise stress test (Bruce protocol) in 28 chronic cocaine users

	Mean	S.D.
Baseline heart rate (beats/min)	87	14.0
Peak heart rate (beats/min)	173	7.8
Peak increase in heart rate (beats/min)	86	15.0
Baseline systolic blood pressure (mm Hg)	113	12.0
Peak systolic blood pressure (mm Hg)	171	20.7
Peak increase in systolic blood pressure (mm Hg)	59	20.5
Baseline rate-pressure product (beats/min*mm Hg)	9841	2010
Peak rate-pressure product (beats/min*mm Hg)	29602	4244
Peak increase in rate-pressure product (beats/min*mm Hg)	19761	4333
Total time of test (min)	10.9	1.6
Reached predicted heart rate? (% yes)	96%	

Table 3

Cardiovascular response to treadmill exercise stress test (Bruce protocol) and to IV cocaine challenge in 9 chronic cocaine users

	Cocaine 25 mg (n = 9)	Cocaine 50 mg (n = 6)
Heart rate increase during stress test (bpm)	91.6 (15.1)	89.2 (17.2)
Heart rate increase during cocaine infusion (bpm)	33.3 (16.2)	30.8 (14.1)
Difference in heart rate increase (bpm)	58.2 (15.0)	58.3 (21.1)
p-value for difference	$p = 2.66 \times 10^{-6}$	$p = .0011$
Systolic blood pressure increase during stress test (mm Hg)	55.3 (25.9)	47.0 (17.9)
Systolic blood pressure increase during cocaine infusion (mm Hg)	27.1 (14.9)	31.0 (11.9)
Difference in systolic blood pressure increase (mm Hg)	28.2 (33.3)	16.0 (24.6)
p-value for difference	$p = .03$	$p = .17$
Rate-pressure product increase during stress test (beats/min*mm Hg)	20270 (5535)	18281 (3410)
Rate-pressure product increase during cocaine infusion (beats/min*mm Hg)	6452 (3169)	6625 (2069)
Difference in rate-pressure product increase (beats/min*mm Hg)	13817 (4985)	11655 (4887)
p-value for difference	$p = 3.3 \times 10^{-5}$	$p = .0021$
Total time for stress test (min)	10.8 (1.4)	10.3 (1.2)
Time to peak heart rate during cocaine infusion (min)	5.3 (4.6)	8.8 (3.8)
Difference in time to peak heart rate (min)	5.5 (5.6)	1.4 (4.6)
p-value for difference	$p = .02$	$p = .48$

bpm = beats per minute.

Data presented as mean (standard deviation).