Exaggerated Pressor Response to Treadmill Exercise in Chronic Cocaine Abusers With Left Ventricular Hypertrophy

Carlos G. Cigarroa, MD; James D. Boehrer, MD; M. Elizabeth Brickner, MD; Eric J. Eichhorn, MD; and Paul A. Grayburn, MD

Background. Chronic cocaine abuse has been associated with a high prevalence of left ventricular hypertrophy (LVH) in normotensive individuals at rest. This study was conducted to determine whether chronic cocaine abusers with LVH would manifest an exaggerated pressor response to treadmill exercise.

Methods and Results. Forty-nine normotensive chronic cocaine abusers underwent Bruce protocol treadmill exercise testing until they attained 85% maximum predicted heart rate. A peak exercise systolic blood pressure ≥210 mm Hg was defined as abnormal. In addition, they underwent two-dimensional echocardiography and had left ventricular mass determined by the area–length method. LVH was defined as left ventricular mass ≥105 g/m² and a posterior wall thickness ≥1.2 cm. Age- and race-matched control subjects also underwent echocardiography and exercise testing. Group differences in peak exercise blood pressure in cocaine abusers with LVH, cocaine abusers without LVH, and control subjects were assessed by ANOVA. Groups were similar concerning age, race, heart rate, resting blood pressure, body surface area, and exercise duration. LVH was present in 16 of 49 (33%) cocaine abusers and three of 30 (10%) control subjects (p=0.02). Of the 16 cocaine abusers with LVH, 10 (63%) had peak exercise blood pressures ≥210 mm Hg, and three others had exercise blood pressures of 200 mm Hg. Therefore, peak exercise systolic blood pressure was significantly higher in cocaine abusers with LVH than in all other groups (p=0.0001).

Conclusions. Chronic cocaine abusers with LVH manifest an exaggerated pressor response to treadmill exercise. These data suggest that chronic cocaine abuse predisposes a subset of individuals to a heightened pressor response to a given sympathetic stimulus such as exercise and that this may contribute to the pathogenesis of LVH in chronic cocaine abusers. (Circulation 1992;86:226–231)

Key Words • cocaine • left ventricular hypertrophy • exercise test • echocardiography

Cocaine abuse has been associated with several acute cardiovascular complications,1–3 which include myocardial infarction and sudden death. Few data, however, exist concerning the ability of cocaine to cause chronic cardiovascular disease. We recently demonstrated a high prevalence of concentric left ventricular hypertrophy (LVH) in chronic cocaine abusers.4 LVH is known to have adverse prognostic implications in hypertension,5–6 and could be important in potentiating the ischemic and arrhythmogenic properties of cocaine. The long-term consequences of cocaine-induced LVH are not known, nor has the mechanism whereby cocaine induces LVH been established.

It is well known that cocaine is a sympathomimetic agent that acutely increases blood pressure7–10 and may precipitate hypertensive crisis.11,12 Moreover, chronic cocaine abuse has been associated with depletion of dopamine stores,13,14 which is a factor that may enhance sensitivity to α-adrenergic vasoconstriction.15 We propose that chronic cocaine abusers have an exaggerated pressor response to sympathetic stimuli (i.e., cocaine, stress, exercise), and that this may be related to the development of LVH. An association between an exaggerated pressor response to treadmill exercise and LVH has been previously demonstrated in normotensive men.16 Accordingly, the following study was undertaken to test the hypothesis that chronic cocaine abusers with LVH manifest an abnormally high blood pressure response to treadmill exercise.

Methods

Study Population

The patient population consisted of 49 normotensive men with a history of chronic cocaine abuse who were enrolled in the inpatient drug dependence treatment program at the Dallas Veterans Affairs Medical Center. Participation in this program requires abstinence from drug usage. Therefore, immediately upon admission, patients were instructed to refrain from drug usage, and this was documented by urine toxicity screens on admission and weekly thereafter. Each patient underwent a thorough history (including date of last cocaine use) and physical examination. Heart rate and blood pres-
sure were taken daily by a physician assistant with an automated cuff (Dinamap 845XT, Criticon, Tampa, Fla.).

Patients entering the drug dependence treatment program were recruited into this study if they were admitted for cocaine addiction (as opposed to heroin addiction with occasional cocaine use) and if none of the following exclusion criteria were present: 1) any resting systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg as determined by a physician assistant, 2) history of cardiovascular disease or use of antihypertensive medication, 3) technically inadequate echocardiography, 4) inability to perform treadmill exercise test, or 5) history of weight lifting or exercise endurance training, which are factors that have been associated with increased left ventricular mass.17–19 There were 41 blacks and eight whites ranging in age from 20 to 43 years (mean, 35.5 ± 5 years). These were not the same subjects in whom we previously reported the association between chronic cocaine abuse and LVH.4 Duration of cocaine abuse ranged from 9 months to 16 years (mean, 5.0±4.1 years). The amount of cocaine used was roughly quantified in terms of money spent on cocaine and ranged from $40 to $2,100 per week (mean, $432±505). Although multiple drug usage was common, cocaine was the predominant substance abused in all cases and the specific substance for which they sought drug rehabilitation. Written informed consent was obtained in all subjects. The control population consisted of 30 normal, healthy male volunteers who were age and race matched to the first 30 cocaine subjects enrolled in the study. All control subjects denied illicit drug use and had none of the above exclusion criteria.

**Echocardiography**

All subjects underwent two-dimensional echocardiography in the left lateral decubitus position with a Vingmed CFM 700 instrument with a 3.0-MHz transducer. Standard parasternal long-axis, parasternal short-axis at midventricular level, apical four-chamber, and apical two-chamber images were acquired and recorded on VHS tape for subsequent analysis. All echocardiographic measurements were made by an experienced observer who was unaware of the cocaine history or the exercise test results. Left ventricular end-systolic and end-diastolic dimensions, posterior wall thickness, septal wall thickness, and left atrial dimension were measured according to the recommendations of the American Society of Echocardiography.20 Left ventricular mass was quantified by the area-length method as recommended by the American Society of Echocardiography.20

Briefly, the areas encompassed by the endocardial (A_e) and epicardial (A_i) surfaces of the left ventricle were traced at end diastole. Left ventricular length (L) at end diastole was measured from the apical four-chamber view. Mean left ventricular wall thickness (t) was calculated from A_e and A_i as

\[
t = \sqrt{\frac{A_i}{\pi}} - \sqrt{\frac{A_e}{\pi}}
\]

Left ventricular mass (LVM) was then calculated from the formula20

\[
LVM = 1.05\left[\frac{5}{6} A_e (L+t) - \frac{5}{6} A_c (L)\right]
\]

For each subject, left ventricular mass was indexed for body surface area. Concentric LVH was defined as a posterior wall thickness ≥1.2 cm and a left ventricular mass index ≥105 g/m², which is 2 SD above the mean value for left ventricular mass index in young healthy men in our laboratory.4 The values for left ventricular mass index in our laboratory are nearly identical to those of other laboratories studying healthy adults by two-dimensional echocardiography.21,22 It is important to note that M-mode studies usually use a higher threshold value (134 g/m²) to define LVH.23 Although M-mode echocardiography, however, may be appropriate for large-scale population-screening studies, it tends to overestimate left ventricular mass and is less suited to evaluation of individual subjects.20

**Exercise Testing Protocol**

Subjects underwent treadmill exercise testing with a Marquette Case I System (Marquette Electronics, Milwaukee, Wis.) with the standard Bruce protocol.24 All subjects exercised until they reached 85% of maximum heart rate predicted for their given age as defined by Ellestad.25 No subject had chest pain or ECG changes of ischemia during exercise. Systolic blood pressure was monitored at 2-minute intervals by sphygmomanometer by an exercise technician with over 15 years' experience of blood pressure recording during clinical exercise testing. Importantly, the technician was deliberately not made aware of the purpose of the study nor was she aware of the results of echocardiography. An abnormal peak exercise systolic blood pressure response was defined as ≥210 mm Hg, based on previous normal control values for young, healthy men.16,25

**Statistical Methods**

All data are expressed as mean ± 1 SD. An F ratio was calculated by ANOVA to determine the significance of group differences in the peak exercise blood pressure in cocaine abusers with LVH, cocaine abusers without LVH, and control subjects. ANOVA also was used to assess group differences in the other dependent variables listed in Table 1. Student's t test was used to compare duration of cocaine abuse, amount of cocaine used, and time interval from last reported cocaine use with exercise testing in the cocaine abusers with and without LVH. A value of p ≤0.05 was considered statistically significant.

**Results**

Table 1 shows the clinical characteristics and echocardiographic results of all subjects studied. No significant difference existed among groups for the following characteristics: age, heart rate, resting systolic and diastolic blood pressures, body surface area, left ventricular or left atrial dimensions, or duration of exercise. As expected, left ventricular septal and posterior wall thickness and left ventricular mass index were significantly increased in patients with LVH as compared with those without LVH. LVH was present in 16 of 49 (33%) cocaine abusers and three of 30 (10%) controls (p = 0.02).

The treadmill exercise tests were performed from 1 to 49 days after the last reported use of cocaine. However,
there was no difference in time from the last reported cocaine use to exercise testing between cocaine abusers with LVH and cocaine abusers without LVH (14.2±15.3 versus 12.8±11.6 days, p=0.717). As shown in Figure 1, there was no relation between peak exercise blood pressure and the time since the last reported cocaine use, which suggests that cocaine withdrawal had no significant effect on exercise blood pressure. Moreover, exaggerated blood pressure responses were present in four of six cocaine abusers with positive urine samples for cocaine at the time of the exercise test.

There was no difference in the duration of cocaine abuse between cocaine abusers with LVH and cocaine abusers without LVH (4.8±4.0 versus 5.1±4.2 years, p=0.828), nor was there a difference in amount of cocaine used ($527±592 versus $378±450 per week, p=0.353).

Figure 2 depicts individual values for peak blood pressure response to exercise in the different groups. Peak exercise systolic blood pressure was significantly higher in cocaine subjects with LVH than in cocaine abusers without LVH or control subjects (F=14.97, p=0.0001). Therefore, 10 of 16 (63%) cocaine abusers with LVH had a peak systolic blood pressure ≥210 mm Hg. Three other patients in this group had a peak exercise blood pressure of 200 mm Hg. Conversely, only three of 33 (9%) cocaine abusers without LVH and two of 30 (7%) normal subjects had an exaggerated pressor response.
response to exercise. Three normal subjects had LVH and a normal blood pressure response to exercise.

The temporal relation of systolic blood pressure during exercise for the different groups is shown in Figure 3. There was no significant difference in systolic blood pressure at baseline, 2 minutes into exercise, or 4 minutes into exercise. However, from 6 minutes onward, systolic blood pressure was significantly higher in the cocaine abusers with LVH than in cocaine abusers without LVH or control subjects. There were no significant differences in systolic blood pressure between cocaine abusers without LVH and control subjects at any point during the exercise test.

**Discussion**

This study clearly demonstrates that chronic cocaine abusers with LVH manifest an exaggerated pressor response to treadmill exercise. Moreover, these data corroborate previous findings that associate chronic cocaine abuse with a high prevalence of LVH. Although the mechanism by which cocaine induces LVH has not been established, these data suggest that intermittent hypertension may play an important role. Gott diener et al. have shown a high prevalence of LVH in normotensive men with an exaggerated pressor response to treadmill exercise. As pointed out by Devereaux, an exaggerated pressor response to exercise may represent a "bioassay" identifying a subset of patients with intermittent hypertension during routine daily activities who are prone to develop LVH. Conversely, LVH may augment the pressor response to exercise or other activities. Although recent studies suggest that the relation between exercise blood pressure and LVH is confounded by age, resting systolic blood pressure, and body surface area, there was no significant difference in these variables in our study. Therefore, our data suggest that chronic cocaine abuse predisposes a subset of patients to a heightened pressor response to given sympathetic stimuli (cocaine, stress, exercise), and that this response probably contributes to the pathogenesis of cocaine-related LVH.

The mechanism by which chronic cocaine abuse causes an exaggerated pressor response is unknown. One possible mechanism to explain this phenomenon has been termed "the dopamine depletion hypothesis." Chronic cocaine administration in animals results in diminished levels of tyrosine hydroxylase, which is the rate-limiting enzyme in the formation of dopamine. In addition, synaptic dopamine levels in the central nervous system have been shown to be depleted during withdrawal from chronic cocaine treatment. Dopamine specifically stimulates two different receptors: Receptor type 1 is located postsynaptically on vascular effector cells in renal, coronary, and cerebral arteries and mediates vasodilatation, whereas receptor type 2 exists on postganglionic sympathetic nerve terminals and inhibits norepinephrine release. Accordingly, it has been postulated that dopamine depletion in chronic cocaine abusers may lead to a heightened response to sympathetic stimuli.

Another mechanism by which cocaine may lead to an exaggerated pressor response to exercise is altered baroreflex control of blood pressure. Andrenes et al. have shown that cocaine depresses aortic arch baroreceptor discharge in an isolated rat aortic arch. This, however, may have been caused by the local anesthetic effects of cocaine in an in vitro preparation. It is not known whether chronic or acute cocaine administration alters baroreflex function in the intact organism.

Intermittent hypertension is not the only mechanism by which cocaine could result in LVH. Cocaine is a sympathomimetic agent that inhibits norepinephrine reuptake at presynaptic nerve terminals. It has been shown that norepinephrine stimulates myofibrillar protein synthesis and cell hypertrophy in cultured rat cardiocytes. In addition, Laks et al. found that chronic infusion of subhypertensive doses of norepinephrine promoted LVH in dogs. Human myocardium, however, contains few α-adrenergic receptors, which is a finding that casts some doubt as to whether cocaine promotes LVH by α-adrenergic stimulation of the myocardium. Moreover, the characteristic cardiac lesion in pheochromocytoma is patchy myocardial necrosis, although ventricular hypertrophy also has been reported. Finally, cocaine possibly could exert a direct trophic effect on myocardium.

**Limitations**

Several limitations must be considered in interpreting the results of this study. Foremost among these is the possibility that the exaggerated pressor response observed in this study may be related to cocaine withdrawal. This, however, is unlikely for several reasons. First, there was no relation between peak exercise blood pressure and the time since the last reported use of cocaine (Figure 1). Second, there was no difference in time from the last reported cocaine use to exercise testing between cocaine abusers with LVH and cocaine abusers without LVH (14.2±15.3 versus 12.8±11.6 days, p=0.717). Third, four of six patients with positive urine samples for cocaine at the time of their exercise test had exaggerated blood pressure responses. Finally, none of the 16 patients who had positive urine samples on
admission displayed physical signs of substance withdrawal, which includes no significant changes in daily heart rate and blood pressure as recorded by the physician assistant.

Another possibility is that the exaggerated pressor response could have been related to residual effects of cocaine or its metabolites. As noted, four of six patients with positive urine samples at the time of their exercise test had an exaggerated pressor response to exercise. Although it is highly improbable that cocaine withdrawal could have accounted for the elevated exercise blood pressure in these four subjects, residual cocaine effects may have been important. Six other subjects with an exaggerated pressor response, however, underwent exercise testing at least 10 days after their last use of cocaine. Given the short half-life of cocaine, it seems unlikely that residual cocaine effects could have caused the exaggerated pressor response in these subjects. Finally, the lack of any temporal relation between exercise blood pressure and the last use of cocaine (Figure 1) strongly argues against residual cocaine effects as the cause of the exaggerated pressor response seen in this study.

Another limitation is that the exaggerated pressor response was documented at only one point in time. Accordingly, ambulatory blood pressure monitoring must be performed to document whether this response occurs with regularly recurring stress during daily activities.

Blood pressure measurements during exercise were made with arm cuff sphygmomanometry. Although invasive blood pressure determination is more accurate during exercise, it was not feasible for this study. The technician recording the exercise blood pressure was blinded to the nature of the study. Accordingly, small errors in blood pressure determination would have been randomly distributed between groups and would not have influenced the outcome of the study.

The possibility that these findings are caused by cocaine-induced dopamine depletion remains speculative, as there is no direct clinical measure of total body or cardiovascular dopamine stores. Although dopamine depletion has been shown in the central nervous system of animals subjected to chronic cocaine administration, cocaine use may promote the development of LVH by mechanisms other than intermittent hypertension, such that the exaggerated blood pressure response is a secondary phenomenon. Further investigation is needed to delineate the temporal relation among chronic cocaine abuse, intermittent hypertensive responses to exercise or stress, and LVH.

Conclusions

Chronic cocaine abusers with LVH manifest an exaggerated pressor response to treadmill exercise. These data suggest that chronic cocaine abuse predisposes a subset of individuals to a heightened pressor response to a given sympathetic stimulus such as exercise, and that this may contribute to the pathogenesis of LVH. Further studies will be required to confirm this hypothesis and to provide insight into the physiological changes resulting in this exaggerated pressor response.

Acknowledgments

The authors thank Arvella Peters for performing the echocardiograms and Velma Bean for her technical assistance with the exercise tests.

References

Exaggerated pressor response to treadmill exercise in chronic cocaine abusers with left ventricular hypertrophy.

C G Cigarroa, J D Boehrer, M E Brickner, E J Eichhorn and P A Grayburn

_Circulation_. 1992;86:226-231
doi: 10.1161/01.CIR.86.1.226

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/86/1/226

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/