Left Ventricular Hypertrophy Associated With Chronic Cocaine Abuse

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**Background.** This study was performed to determine whether chronic cocaine abuse is associated with left ventricular hypertrophy in humans.

**Methods and Results.** A consecutive series of 40 chronic cocaine abusers 23–44 years old who were enrolled in an inpatient drug rehabilitation program were considered for the study. Subjects with elevated resting blood pressure (n=4) or a history of hypertension (n=3) were excluded. Technically adequate two-dimensional echocardiograms were obtained in 30 cocaine abusers and 30 age- and race-matched normal control subjects. All subjects were men, and the groups were similar with regard to resting blood pressure, height, weight, and body surface area. All echocardiograms were read in blinded fashion, and left ventricular mass was calculated by the area–length method. Left ventricular cavity dimensions and wall motion were normal in all subjects. Left ventricular mass index was higher in the cocaine group (103±24 versus 77±14 g/m², p=0.0001). Posterior wall thickness was increased (1.2 cm or more) in 13 cocaine abusers (43%) compared with four controls (p=0.0099).

**Conclusions.** Chronic cocaine abuse is associated with increased left ventricular mass index and wall thickness. Left ventricular hypertrophy may provide a substrate facilitating the development of myocardial ischemia and/or arrhythmias in cocaine abusers. (Circulation 1991;84:1130–1135)

Cocaine abuse has reached epidemic proportions in the United States. It has been estimated that as many as 30 million Americans have used cocaine at least once and as many as 5 million may be chronic users.1 The use of cocaine has been associated with a variety of potentially lethal cardiovascular events, including angina, myocardial infarction, myocarditis, cardiomyopathy, hypertension, rupture of the ascending aorta, ventricular arrhythmias, and sudden death.2 There are several potential mechanisms by which cocaine may cause cardiovascular events. Cocaine blocks the presynaptic reuptake of norepinephrine and dopamine, thus increasing their post synaptic concentrations and causing sympathetic stimulation.3 Research in animals has shown cocaine to be a potent vasoconstrictor in the peripheral and coronary circulations.4,5 Recent data from our institution have shown that cocaine causes coronary artery vasoconstriction in humans,6 a phenomenon that is abolished by α-adrenergic blockade and potentiated by β-adrenergic blockade.6,7 Furthermore, we have also demonstrated functional and anatomic abnormalities of the coronary artery endothelium in chronic cocaine users,8 factors that may facilitate cocaine-mediated coronary artery vasoconstriction and thrombosis. Cocaine also inhibits membrane sodium channels (a type 1 antiarrhythmic effect) and shortens the ventricular refractory period3,9 (properties that may predispose toward arrhythmias). In animal studies, acute administration of cocaine has been shown to cause depressed left ventricular function,10 and a direct toxic effect of cocaine on the myocardium has also been postulated.11

In the course of examining the coronary arteries of young men dying of cocaine overdose, we encountered marked left ventricular hypertrophy in several patients at our institution, none of whom had any medical condition known to cause left ventricular hypertrophy. Although cocaine could theoretically induce left ventricular hypertrophy by a variety of mechanisms, including chronic adrenergic stimulation of the myocardium or intermittent cocaine-induced blood pressure elevation, an association between left ventricular hypertrophy and cocaine use has not been clearly established in humans. The purpose of the present study, therefore, was to use echocardiographic techniques to...
determine the prevalence of left ventricular hypertrophy in chronic cocaine users compared with age- and race-matched controls.

Methods

Patient Recruitment

Forty consecutive subjects ranging in age from 23 to 44 years were recruited from the inpatient Drug Dependence Treatment Program of the Dallas Veterans Affairs Medical Center. This program involves a 28-day admission during which the patients are fully ambulatory and actively involved in a variety of group activities, sports, and counseling sessions. Vital signs are taken daily and recorded on the chart. After informed consent, each subject was interviewed using a questionnaire to determine frequency and duration of cocaine use, method of drug ingestion, amount of cocaine used (in dollars spent per day), use of other drugs (including ethanol), presence of other known medical conditions, and use of prescription medications. No patient had a history of any known cardiovascular complications related to their use of cocaine. Patients were specifically excluded if they had a history of hypertension or other cardiovascular disease or were taking antihypertensive medications.

Resting blood pressure was obtained in all subjects on admission to the Drug Dependence Treatment Program, daily thereafter, and at the time of the echocardiographic study. Four patients were excluded from further participation because of elevated resting blood pressures, defined as systolic blood pressure of more than 140 mm Hg or diastolic blood pressure of more than 90 mm Hg. Three other patients were excluded because of a prior history of hypertension, and three were excluded because of technically inadequate echocardiograms, leaving a total of 30 chronic cocaine abusers completing the study. A control group consisting of 30 normal, healthy volunteers with no history of illicit drug use, hypertension, or cardiovascular disease was recruited from the hospital housestaff and employees. The control subjects were individually matched to the cocaine subjects with regard to both age and race. No subject in the control group had resting hypertension at the time of the echocardiographic study. Subjects with a history of weight-lifting or endurance exercise training were excluded from both groups because these activities have been shown to be associated with increased left ventricular mass.12–14

Echocardiography

All subjects underwent two-dimensional echocardiography in the left lateral decubitus position using a Vingmed CFM 700 instrument with a 3.0-MHz transducer. By phantom calibration, this transducer has an axial resolution of 1 mm and a lateral resolution of 3 mm. Measurement of vertical distance using the Vingmed analysis software was also evaluated by phantom and was highly accurate with a 2% coefficient of variation.

Gain settings were adjusted to optimize visualization of the left ventricular endocardial contours while avoiding excessive gain artifact. Images were obtained from standard echocardiographic views, including parasternal long-axis, parasternal short-axis at the midventricular level, apical four-chamber, and apical two-chamber views. All images were recorded on ½-in. VHS tape and subsequently analyzed in blinded fashion by an experienced observer. Left ventricular septal and posterior wall thicknesses at end diastole were measured from the parasternal long-axis view at the tips of the mitral leaflets according to the recommendations of the American Society of Echocardiography.15 Two-dimensional echocardiographic estimation of left ventricular mass was performed using the 5/6 area–length method.15 Accordingly, the areas encompassed by the left ventricular epicardial and endocardial borders were traced at end diastole from the parasternal short-axis view at the midventricular level. Left ventricular length (L) at end diastole was measured from the apical four-chamber view. Myocardial thickness (t) and short-axis radius (b) were calculated from the areas of the epicardial (A1) and endocardial (A2) contours according to the following formulas15:

\[ b = \sqrt{\frac{A_2}{\pi}} \quad \text{and} \quad t = \sqrt{\frac{A_1}{\pi}} - b \]

Left ventricular mass (LVM) was then calculated by the following formula15:

\[ \text{LVM} = 1.05[\frac{5}{6}A_1(L + t) - \frac{5}{6}A_2(L)] \]

Interobserver and intraobserver variabilities for the measurement of left ventricular mass were assessed in a subgroup of 15 subjects. Echocardiograms in these subjects were read in blinded fashion by a second observer (J.W.) and by the primary observer (G.P.) a second time. Correlations between values for left ventricular mass were good for both interobserver (r=0.91, SEE=11 g) and intraobserver (r=0.95, SEE=10 g) measurements.

Statistical Analysis

Data are expressed as mean±1 SD. Left ventricular mass was indexed for body surface area, and differences between cocaine and control groups were analyzed by Student’s t test. An F ratio was calculated by two-factor analysis of variance to determine the effects of cocaine, alcohol, and their combination on left ventricular mass index. For grouping purposes, increased alcohol consumption was defined as more than 210 ml/wk because this value has been shown to be associated with increased left ventricular mass index in men in the Framingham Study.16 The number of subjects in each group with left ventricular hypertrophy defined as posterior wall thickness of more than 1.2 cm was compared by contingency table analysis using the \( \chi^2 \) test. A probability value of 0.05 or less was considered statistically significant.
Table 1. Clinical Characteristics and Echocardiographic Results

<table>
<thead>
<tr>
<th></th>
<th>Cocaine abusers (n=30)</th>
<th>Normal controls (n=30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35±6</td>
<td>35±6</td>
<td>0.932</td>
</tr>
<tr>
<td>Race (B/W)</td>
<td>21/9</td>
<td>21/9</td>
<td>1.0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>179±7</td>
<td>179±6</td>
<td>0.800</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79±10</td>
<td>79±9</td>
<td>0.918</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.97±0.15</td>
<td>1.97±0.13</td>
<td>0.935</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>117±11</td>
<td>121±6</td>
<td>0.069</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>75±7</td>
<td>77±6</td>
<td>0.086</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>4.5±0.3</td>
<td>4.5±0.5</td>
<td>0.879</td>
</tr>
<tr>
<td>LVESD (cm)</td>
<td>3.0±0.5</td>
<td>3.1±0.5</td>
<td>0.439</td>
</tr>
<tr>
<td>FS (%)</td>
<td>34±9</td>
<td>32±7</td>
<td>0.220</td>
</tr>
<tr>
<td>PWT (cm)</td>
<td>1.12±0.17</td>
<td>1.01±0.13</td>
<td>0.0056</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>103±24</td>
<td>77±14</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

B, black; W, white; BSA, body surface area; BP, blood pressure; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; FS, fractional shortening; PWT, posterior wall thickness; LVMI, left ventricular mass index.

Results

Characteristics of the study population are shown in Table 1. There were no group differences in terms of height, weight, or body surface area. The control group tended to have higher systolic and diastolic blood pressures than the cocaine group, although this was not statistically significant. The duration of cocaine abuse ranged from 1 month to 20 years (median, 36 months) at a cost of $10–300 per day (median, $80 per day). Of the 30 cocaine abusers, 15 admitted to intravenous use, and eight of the 15 also inhaled or smoked cocaine. Most of the abusers also used other drugs, including narcotics (n=9), amphetamines (n=8), marijuana (n=12), and alcohol (n=18). Only eight subjects had increased alcohol consumptions (more than 210 ml/wk). Importantly, in each subject, cocaine was the most frequently abused substance and the specific substance for which they sought drug rehabilitation treatment.

Echocardiographic images of sufficient quality to calculate left ventricular mass were obtained in 30 cocaine users and 30 controls. No subject had left ventricular dilatation, segmental wall motion abnormalities, or evidence of valvular pathology on two-dimensional echocardiography. There were no significant differences in left ventricular end-diastolic dimension, left ventricular end-systolic dimension, or percent fractional shortening between the cocaine and control groups (Table 1).

Left ventricular mass index was significantly higher in the patients with a history of cocaine abuse than in the controls (103±24 versus 77±14 g/m², p=0.0001) (Figure 1). Three subjects had markedly elevated left ventricular mass indexes, two of whom had each used intravenous cocaine for more than 6 years. Both of these subjects consistently had blood pressures of approximately 110/70 mm Hg. The third subject, a heavy drinker with a blood pressure of 124/86 mm Hg, may have had left ventricular hypertrophy resulting from undetected hypertension or alcohol. However, even if all three of these subjects were excluded from analysis as potential outliers, left ventricular mass index was still significantly higher in the cocaine group than in the controls (97±16 versus 77±14 g/m², p=0.0001).

Left ventricular mass index was more than 2 SDs from the mean value of the control group (more than 105 g/m²) in 13 of 30 cocaine abusers (43%). Of these 13 cocaine abusers with echocardiographic evidence of left ventricular hypertrophy, only three had increased alcohol consumptions (more than 210 ml/wk), and six were nondrinkers. By two-factor analysis of variance, increased alcohol consumption was not independently associated with increased left ventricular mass index (F=0.099, p=0.754), nor was a group interaction between cocaine and alcohol present (F=0.71, p=0.404). Thus, the association of left ventricular hypertrophy with cocaine abuse did not appear to be influenced by concomitant alcohol abuse.

As shown in Figure 2, posterior wall thickness was significantly greater in the cocaine group than in the controls (1.12±0.17 versus 1.01±0.13 cm, p=0.0056). Increased posterior wall thickness (1.2 cm or more) was found in 13 cocaine abusers (43%) compared with four controls (13%) (χ²=6.65, p=0.0099). No relation was found between left ventricular hypertrophy and either route of cocaine administration or quantity of cocaine. However, 12 of the 13 cocaine users with increased wall thickness used cocaine for more than 12 months (χ²=5.43, p=0.0197), suggesting that duration of use may be associated with left ventricular hypertrophy.

Discussion

Results from the present study demonstrate that chronic cocaine abuse is associated with increased
left ventricular mass and wall thickness. Although this association has not been previously described, several autopsy studies have reported increased heart weight in patients with elevated cocaine levels at the time of death.

Virmani et al. reported autopsy results in 40 patients with detectable levels of cocaine or its metabolites and found increased heart weight in eight of these patients. However, there was no difference in mean heart weight between the 40 patients with cocaine-associated deaths and 27 victims of sudden traumatic death who served as control subjects. Although such data appear to contradict our findings, it must be emphasized that retrospective autopsy series, which cannot exclude hypertension during life in either the cocaine or the control group, neither confirm nor refute the hypothesis that cocaine promotes the development of left ventricular hypertrophy. Our study, in which subjects with elevated resting blood pressure or a history of hypertension were excluded from each group, demonstrates higher left ventricular mass and wall thickness in cocaine abusers than in age- and race-matched controls.

The finding of increased left ventricular mass and wall thickness with normal left ventricular chamber size indicates that cocaine is associated with concentric left ventricular hypertrophy. Conversely, the increased left ventricular mass associated with alcohol is generally associated with dilated cardiomyopathy and eccentric hypertrophy, although concentric hypertrophy can also be seen. Our data did not demonstrate an effect of alcohol on increased left ventricular mass, nor was an interaction between cocaine and alcohol present.

Although these data establish an association between cocaine abuse and left ventricular hypertrophy, causation has not been proven, nor has a mechanism been defined. It could be postulated that by blocking norepinephrine reuptake, cocaine may directly stimulate myocardial α-adrenergic receptors and thus facilitate the development of left ventricular hypertrophy. Studies in animals suggest that α-adrenergic stimulation may be a factor in the development of left ventricular hypertrophy. α1-Adrenergic stimulation elicits myofibrillar protein synthesis and cell hypertrophy in cultured neonatal rat cardiac myocytes. Furthermore, chronic norepinephrine administration induces left ventricular hypertrophy in dogs. In the guinea pig, α1-adrenergic blockade prevents the development of left ventricular hypertrophy under conditions of pressure overload, although it is not known whether this is by a direct effect on myocardial protein synthesis or a secondary effect of lowering afterload. Nevertheless, the role of α-adrenergic stimulation on myocardial hypertrophy in humans is doubtful because the density of α-adrenergic receptors on human myocardial cells is very low. Furthermore, patients with chronic catecholamine stimulation secondary to pheochromocytoma develop a cardiomyopathy characterized by patchy myocardial necrosis, although hypertrophy may also be seen.

An alternative explanation for the association between cocaine abuse and left ventricular hypertrophy is acute intermittent blood pressure elevation after cocaine ingestion. It is well known that acute cocaine administration, even in modest doses, results in blood pressure elevation. Furthermore, Gottdiener et al. recently identified left ventricular hypertrophy in 64% of normotensive men with an abnormal blood pressure response to exercise, suggesting that intermittent blood pressure elevation may be associated with left ventricular hypertrophy. It could also be postulated that chronic β1-adrenergic stimulation of the juxtaglomerular apparatus could activate the renin-aldosterone-angiotensin system, resulting in hypertension. The lack of resting hypertension in the majority of cocaine subjects recruited for this study argues against this possibility. Other potential mechanisms, such as a direct effect of cocaine (or a contaminant in “street” cocaine) on cellular hypertrophy, cannot be excluded on the basis of these data. Thus, further research is needed to elucidate the mechanism whereby cocaine abuse results in increased left ventricular mass and wall thickness.

**Clinical Importance**

Echocardiographic evidence of left ventricular hypertrophy has been associated with an increased risk of cardiovascular events and increased mortality in several studies. Accordingly, it is attractive to speculate that left ventricular hypertrophy in cocaine abusers provides a substrate that facilitates the development of cardiovascular events, including myocardial ischemia and arrhythmias. Left ventricular hypertrophy is associated with increased coronary flow reserve, decreased subendocardial perfusion, and increased myocardial oxygen consumption, factors that may favor the development of myocardial

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**FIGURE 2.** Plot showing distribution of values for posterior wall thickness for cocaine abusers and control subjects. Error bars show mean ± 1 SD.
ischemia in the setting of cocaine-induced coronary artery vasoconstriction and/or thrombosis. Furthermore, it has been postulated that cocaine-induced cardiac arrhythmias are more likely to occur in the setting of underlying myocardial abnormalities such as infarction, ischemia, or contraction band necrosis. The presence of left ventricular hypertrophy may provide an anatomic substrate that potentiates the arrhythmogenic properties of cocaine.

Limitations

Although our data demonstrate an association between cocaine use and increased left ventricular mass, several limitations must be considered. “Street” cocaine may contain a variety of other substances and may, in some cases, have no active cocaine at all, making it virtually impossible to obtain an accurate estimate of dosage by history. Thus, a relation between the amount of cocaine use and the degree of left ventricular hypertrophy could not be established. Furthermore, we cannot exclude the possibility that a contaminant was responsible for the development of left ventricular hypertrophy. However, even if this were the case, the point remains that left ventricular mass index is increased in cocaine abusers.

The threshold value for left ventricular hypertrophy in this study (left ventricular mass index, more than 105 g/m²) is somewhat lower than those reported in studies using M-mode techniques. However, echocardiographic left ventricular mass estimates, although well validated, may vary somewhat depending on the exact method used, instrument and technical factors, and patient population studied. Our study population was very young and excluded patients with hypertension or other cardiovascular disease, factors that would tend to lower the group mean left ventricular mass. Furthermore, our values for left ventricular mass index in normal subjects were strikingly similar to those reported by others using two-dimensional echocardiographic techniques. However, even if our threshold value were artificially low, the fact remains that left ventricular mass index is a continuous variable, not a binary one, and was significantly higher in cocaine abusers than in normal subjects.

Because our patients were recruited from an inpatient drug rehabilitation program, there is an inherent selection bias toward at least moderate cocaine use. Thus, the prevalence of left ventricular hypertrophy seen in our study may be higher than that in occasional users. Conversely, very heavy users may have more left ventricular hypertrophy than was present in our population. Finally, this study involved determination of left ventricular mass at a single point in time. Therefore, it is uncertain whether left ventricular mass progressively increases with continued cocaine abuse or, alternatively, whether left ventricular mass regresses with abstinence from cocaine.

Conclusions

Chronic cocaine abuse is associated with increased left ventricular wall thickness and mass index. Left ventricular hypertrophy may provide a substrate facilitating the development of myocardial ischemia and/or arrhythmias after cocaine ingestion. Further research is needed to elucidate the mechanism whereby cocaine promotes myocardial hypertrophy.

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**KEY WORDS** • cocaine • left ventricular hypertrophy • echocardiography
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