Cocaine Use and the Likelihood of Nonfatal Myocardial Infarction and Stroke

Data From the Third National Health and Nutrition Examination Survey

Adnan I. Qureshi, MD; M. Fareed K. Suri, MD; Lee R. Guterman, PhD, MD; L. Nelson Hopkins, MD

Background—Numerous case series have implicated cocaine use as a cause of both myocardial infarction (MI) and stroke on the basis of the temporal relationship between drug use and event onset. Increasing cocaine use in the US population, especially in younger individuals, mandates a more extensive investigation of this relationship.

Methods and Results—We determined the association of cocaine use with self-reported physician diagnosis of MI or stroke in a nationally representative sample of 10 085 US adults aged 18 to 45 years who participated in the Third National Health and Nutrition Examination Survey. A total of 46 nonfatal MIs and 33 nonfatal strokes were reported. After adjusting for differences in age, sex, race/ethnicity, education, hypertension, diabetes mellitus, cholesterol level, body mass index, and cigarette smoking, persons who reported frequent lifetime cocaine use had a significantly higher likelihood of nonfatal MI than nonusers (odds ratio, 6.9; 95% confidence interval, 1.3 to 58) but not stroke. In this age group, the population-attributable risk percent of frequent cocaine for nonfatal MI was estimated as 25%.

Conclusion—Regular cocaine use was associated with an increased likelihood of MI in younger patients. Approximately 1 of every 4 nonfatal MIs in persons aged 18 to 45 years was attributable to frequent cocaine use in this survey. Behavior modification by public awareness and education may reduce the cardiovascular morbidity associated with cocaine use. (Circulation. 2001;103:502-506.)

Key Words: cocaine ■ stroke ■ myocardial infarction ■ risk factors

Cocaine became available for recreational use in the United States ≈2 decades ago. More than 30 million Americans have tried cocaine once, and 5 million report regular use. With the growing use of cocaine, a better understanding of its effect on cardiovascular diseases is essential. Numerous reports have suggested that cocaine use may be associated with myocardial infarction (MI) and stroke. The majority of this evidence is based on the temporal proximity of cocaine use and MI or stroke. Few case-control studies have suggested conflicting results. Some studies were performed at single centers and were therefore influenced by the socioeconomic status and age distribution of the population served by these centers. To avoid these potential confounding factors, data from the Third National Health and Nutrition Examination survey (NHANES III), a large population-based study, were used to examine the independent association between cocaine use and nonfatal stroke and MI.

Methods

NHANES III was conducted by the Centers for Disease Control and Prevention between 1988 and 1994 to estimate the prevalence of common chronic conditions and associated risk factors in the US population. The NHANES III participants included ~40 000 persons aged ≥2 months who were selected from the total civilian noninstitutionalized population in the 50 states of the United States. The sample was selected from households in 81 counties across the United States. The sample was taken from 89 locations that were randomly divided into 2 sets. One set was allocated to the first 3-year survey period (1988 to 1991) and the other set to the second 3-year period (1991 to 1994). All households and eligible group quarters in the sample segments were listed, and a subsample was designated for screening to identify potential sample persons. The subsampling rates enabled the production of a national, approximately equal, probability sample of households in most of the United States, with higher rates for the geographic strata with high Mexican populations. The black and Mexican populations were oversampled to obtain statistically reliable estimates of the 2 largest minority groups in the United States. In addition, the survey included oversampling of children and the elderly. Although NHANES III did not oversample the female population, it was designed to include equal numbers of males and females in each age and race/ethnic group. The survey included a household interview, a medical examination in a mobile examination center, a brief household medical examination for those unable to travel to the center, and a phlebotomy to measure vascular disease risk factors including glucose, cholesterol, high-density lipoproteins, triglycerides, and apolipoproteins A-I and B.

Each participant aged 18 to 59 years was asked about lifetime cocaine use in terms of the following 4 responses: never, <10 times, 10 to 100 times, or >100 times. We categorized the participants as...
nonusers if they responded to the lifetime cocaine use question as never used, as infrequent users if they responded as using <10 times, and as frequent users if they reported using cocaine 10 to 100 times or >100 times. Persons were considered nonusers if no response was available for the question. Persons were considered as having had a stroke if they reported that they had been told by a physician that they had suffered a stroke. Persons were considered as having had a MI if they reported that they had been told by a physician that they had suffered a heart attack. Hypertension was defined as the current use of antihypertensive medication or an average blood pressure >140/90 mm Hg. Hyperlipidemia was defined by a serum cholesterol level >200 mg/dL. Diabetes mellitus was defined as an affirmative response to the question “have you ever been told by a doctor that you have diabetes or sugar diabetes?” Although serum glucose measurements were available, the samples were drawn inconsistently in relation to fasting status and, therefore, were not used to define diabetes mellitus.

The data were analyzed for persons aged 18 to 45 years. The small number of persons who used cocaine (n=25) among those aged 46 to 59 years precluded further analysis of this age group. Potential confounding factors in the association between cocaine use and stroke and MI included age, sex, race/ethnicity, education, hypertension, hyperlipidemia, diabetes mellitus, body mass index (weight [kg]/height [m²]), cigarette smoking, and insurance status. χ² tests and ANOVA were used to compare groups according to frequency of cocaine use. To determine whether the likelihood of MI or stroke differed by frequency of cocaine use, multivariate logistic regression analyses were used. The logistic regression model was adjusted for the aforementioned confounding factors. Interactions between cocaine use and other potential confounding factors were tested. No significant interactions were observed in the model.

To estimate the impact of cocaine use on MI or stroke, we calculated the population-attributable risk percent. Population-attributable risk percent expresses the proportion of disease (MI or stroke) in the study population that is attributable to the exposure (cocaine use) and thus could be eliminated if the exposure was eliminated. The population-attributable risk percentage was calculated using the following formula:

\[\text{PAR\%} = \left(\frac{(P_e)(OR-1)}{(P_e)(OR-1) + 1}\right) \times 100\]

where \(\text{PAR\%}\) indicates population-attributable risk percent, \(P_e\) represents the proportion of the population exposed to the risk factor (frequent cocaine user), and \(OR\) indicates odds ratio (multivariate adjusted).

To evaluate the reliability of self-reported information in cocaine and nonco-caine users, we assessed the sensitivity and specificity of self-reported medical conditions for which clinical data were collected as part of NHANES III. Self-reported hypertension was correlated with clinical hypertension, as defined by a blood pressure >140/90 mm Hg or use of antihypertensive medication. Self-reported diabetes mellitus was correlated with clinical diabetes, as defined by a fasting plasma glucose >7.0 mmol/L or use of oral hypoglycemic medication or insulin. Self-reported hyperlipidemia was correlated with clinical hyperlipidemia, as defined by a fasting serum cholesterol level >200 mg/dL or use of antilipemic medication.

### Results

Among the 20,050 participants screened in the NHANES III survey, 10,085 (50.3%) were 18 to 45 years old. The remaining 9,965 (49.7%) survey participants were either ≤17 years of age or >45 years and were excluded from the study. In the 18- to 45-year-old group, the mean age was 30.9 ± 7.9 years, and 4,693 person (46.5%) were men. Table 1 shows the demographic and clinical characteristics of this group. A total of 731 persons (7.2%) reported infrequent use of cocaine, and 532 (5.3%) reported regular use. A higher proportion of men and blacks used cocaine regularly. Educational attainment was lower in persons who used cocaine regularly. Persons who reported regular use of cocaine were more likely to be hypertensive and current smokers. No significant differences were found between cocaine use and any of the following

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cocaine Nonusers (n=8822)</th>
<th>Infrequent Cocaine Users (1–10 times) (n=731)</th>
<th>Frequent Cocaine Users (&gt;10 times) (n=532)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>30.8 ± 8.0</td>
<td>30.6 ± 6.7</td>
<td>32.8 ± 6.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Men</td>
<td>3908 (44)</td>
<td>430 (59)</td>
<td>355 (67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>5474 (62)</td>
<td>487 (67)</td>
<td>275 (52)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Black</td>
<td>2961 (34)</td>
<td>222 (30)</td>
<td>242 (45)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other</td>
<td>387 (4)</td>
<td>22 (3)</td>
<td>15 (3)</td>
<td>0.4</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 y</td>
<td>2889 (33)</td>
<td>248 (34)</td>
<td>149 (28)</td>
<td>0.03</td>
</tr>
<tr>
<td>Medical insurance</td>
<td>6160 (70)</td>
<td>499 (68)</td>
<td>357 (67)</td>
<td>0.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1400 (16)</td>
<td>117 (16)</td>
<td>108 (20)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean body mass index, kg/m²</td>
<td>27 ± 6.2</td>
<td>26 ± 5.9</td>
<td>26 ± 5.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean cholesterol, mg/dL</td>
<td>190 ± 40</td>
<td>190 ± 57</td>
<td>187 ± 58</td>
<td>0.2</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2767 (31)</td>
<td>250 (34)</td>
<td>164 (31)</td>
<td>0.8</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>5270 (60)</td>
<td>218 (30)</td>
<td>93 (17)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Former</td>
<td>1176 (13)</td>
<td>146 (20)</td>
<td>110 (21)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current</td>
<td>2376 (27)</td>
<td>367 (50)</td>
<td>329 (62)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
bities.14 Therefore, these data provide a unique opportunity to based assessments of cocaine use with associated comor-

tions according to use of cocaine.

NHANES III represents one of the first national, population-


topology are attributable to the frequent use of cocaine.

The population-attributable risk percent of frequent co-

caine use in persons aged 18 to 45 years was estimated as 25%, ie, 25% of the MIIs in this segment of the study population are attributable to the frequent use of cocaine.

The sensitivity and specificity of self-reported hypertension was 71% and 92% in cocaine users and 75% and 93% in nonusers, respectively. The sensitivity and specificity of self-reported diabetes mellitus was 56% and 99% in cocaine users and 67% and 98% in nonusers, respectively. The sensitivity and specificity of self-reported hyperlipidemia was 49% and 87% in cocaine users and 51% and 89% in nonusers, respectively. No significant differences were identified between the sensitivity and specificity of self-reported conditions according to use of cocaine.

Discussion

In the younger group of participants, 46 nonfatal MIs (0.5%) and 33 nonfatal strokes (0.3%) were reported. Persons who used cocaine regularly had a significantly higher likelihood of nonfatal MI than nonusers (OR, 6.9; 95% confidence interval [CI], 1.3 to 58; Table 2). The persons who reported infrequent use of cocaine had a lower likelihood of nonfatal MI (OR, 0.1; 95% CI, 0.002 to 0.8). The age- and multivariate-adjusted likelihood for stroke did not show any significant association with either infrequent or regular cocaine use (Table 3).

The population-attributable risk percent of frequent cocaine use in persons aged 18 to 45 years was estimated as 25%, ie, 25% of the MIs in this segment of the study population are attributable to the frequent use of cocaine.

Among persons aged 18 to 45 years, most persons who reported regular cocaine use were men. A higher proportion of blacks reported regular cocaine use. Hypertension and current smoking were more frequent in persons who used cocaine regularly than in nonusers. There were no other differences in the frequency of other cardiovascular risk factors, including diabetes mellitus and cholesterol levels, in groups defined by frequency of cocaine use. Contrary to previous belief, access to health care (as reflected by medical insurance status) was similar in cocaine users and nonusers and did not contribute to an increased likelihood of MI in persons with frequent cocaine use.

We observed that regular use of cocaine predisposed young persons to MI. Recent cocaine use has been observed in patients experiencing MI without and, more frequently, with underlying coronary artery disease.3–7 The first case of MI temporally related to the recreational use of cocaine was described in 1982.4 Galasko et al4 found >250 cases of MI related to cocaine use in the literature. Most data are based on case series consisting of patients with MI associated with the recent use of the drug.5–7 Angiographic findings include normal coronary arteries, vasospasm, or atherosclerotic narrowing. Nunez et al16 demonstrated that regular administration of cocaine in swine can induce acute and chronic MI. Using a self-matched control database on the case-crossover design, the Determinants of Myocardial Infarction Onset Study3 found that the risk of MI was elevated 23.7 times over baseline in the 60 minutes after cocaine use. On the basis of

<p>| TABLE 2. Association Between Cocaine Use and Nonfatal MI in Persons Aged 18 to 45 Years |
|-----------------------------------------------|---------------------------------|------------------------------|-------------------|</p>
<table>
<thead>
<tr>
<th>Sample Size</th>
<th>No. of MIs</th>
<th>Age-Adjusted OR (95% CI)</th>
<th>Multivariate-Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonusers</td>
<td>8822</td>
<td>39 (0.44%)</td>
<td>Reference</td>
</tr>
<tr>
<td>Infrequent users</td>
<td>731</td>
<td>1 (0.14%)</td>
<td>0.5 (0.01–7.8)</td>
</tr>
<tr>
<td>Frequent users</td>
<td>532</td>
<td>6 (1.13%)</td>
<td>6.4 (1.25–53)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, race, insurance status, education, smoking (former and current), diabetes mellitus, hypertension, and hyperlipidemia.

<p>| TABLE 3. Association Between Cocaine Use and Nonfatal Stroke in Persons Aged 18 to 45 Years |
|-----------------------------------------------|---------------------------------|------------------------------|-------------------|</p>
<table>
<thead>
<tr>
<th>Sample Size</th>
<th>No. of Strokes</th>
<th>Age-Adjusted OR (95% CI)</th>
<th>Multivariate-Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonusers</td>
<td>8822</td>
<td>31 (0.35%)</td>
<td>Reference</td>
</tr>
<tr>
<td>Infrequent users</td>
<td>731</td>
<td>1 (0.19%)</td>
<td>0.5 (0.01–7.8)</td>
</tr>
<tr>
<td>Frequent users</td>
<td>532</td>
<td>1 (0.19%)</td>
<td>0.7 (0.01–10.5)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, race, insurance status, education, smoking (former and current), diabetes mellitus, hypertension, and hyperlipidemia.
the above observations, cocaine use has been implicated in the pathogenesis of MI.

The underlying mechanism for the association between regular cocaine use and MI in young persons is not well understood. Cocaine potentiates adrenergic activity by blocking the presynaptic uptake of norepinephrine and dopamine.\(^1\) Increased adrenergic activity subsequently increases myocardial oxygen demand by increasing ventricular contractility and heart rate.\(^1\) Other potential mediators, such as coronary vasoconstriction,\(^19,20\) increase platelet aggregability,\(^21\) and increased plasma concentrations of plasminogen activator inhibitor-1\(^22\) have been suggested as well. Cocaine use in young patients has also been shown to accelerate atherosclerosis.\(^23\) Our study suggests that regular but not infrequent cocaine use plays a critical role in increasing susceptibility to MI. A similar observation was reported by Mittelman et al\(^24\) in the Determinants of Myocardial Infarction Study; the majority of patients who presented with cocaine-related MI were regular and not first-time users. The importance of regular exposure supports the development of underlying chronic pathophysiology as opposed to a transient phenomenon, such as increased adrenergic activity.

We did not observe a relationship between cocaine use, either infrequent or frequent, and nonfatal stroke in persons aged 18 to 45 years. Numerous case series have proposed an association between cocaine use and cerebrovascular disease in young adults.\(^8-11\) In 1990, Kaku and Lowenstein\(^12\) presented the first case-control analysis demonstrating the relationship between recreational drug abuse and stroke in persons aged 15 to 44 years. Cocaine use, including intravenous administration, was implicated in the pathogenesis of stroke in 27 of the 244 patients with stroke. However, their study was limited because it was conducted from 1979 through 1988. Crack cocaine did not become available until 1982.\(^1\) Petitti et al\(^25\) performed a case-control analysis among members of Kaiser Permanente with or without stroke. They reported that use of amphetamines and/or cocaine was a risk factor for stroke in women aged 15 to 44 years. We were previously unable to document a relationship between crack cocaine use (short-term or otherwise) and stroke or cerebral infarction in a retrospective case-control study conducted at a large inner-city public hospital in patients aged 20 to 39 years.\(^26\) The present study also does not support the notion that cocaine use predisposes individuals to nonfatal strokes.

This report is subject to a number of potential limitations. The definitions of MI and stroke were based on self-reported physician diagnoses. O’Mahony et al\(^27\) validated the accuracy of assessing lifetime history of stroke in a random sample of 2000 persons aged \(\geq \)45 years in a mailed questionnaire. Participants were asked whether they ever had a stroke. Response accuracy was confirmed by a medical records review. The question had a sensitivity of 95% and a specificity of 96%. Similarly, a high sensitivity (74% to 100%) and specificity (94% to 99%) have been reported for estimation of prevalent MI by means of mailed questionnaires.\(^28,29\) Previous studies have suggested that self-reported MI in the NHANES surveys is reasonably accurate to justify its use in the assessment of risk factor and prevalence studies. A study was conducted in the early years of the National Health Survey to measure the accuracy and completeness of health interviews.\(^28\) The study concluded that the frequency of underreporting or overreporting was low for heart diseases. Bergmann et al\(^30\) compared interview reports with hospitalization records in 10,523 participants from NHANES I. The interview consisted of the same question for MI as that used in NHANES III in a very similar study population. A true positive rate of 83% (95% CI, 78% to 87%) was observed for the 294 self-reported MIs. The accuracy of self-reports was not influenced by age, sex, alcohol use, or smoking. The reliability of reported data are also supported by the high specificity observed for self-reported hypertension, diabetes mellitus, and hyperlipidemia in NHANES III.

It is possible that individuals underreport the use of cocaine\(^31\) because of the social stigma associated with it. Brown et al\(^32\) evaluated the accuracy of self-reporting cocaine use by interviews and urine toxicology in 234 inpatients. An agreement of 93% was observed between information obtained at interview and urine toxicology. Hollander et al\(^33\) reported that 43 of 60 patients (72%) who tested positive for cocaine admitted to recent use of cocaine in the emergency room. However, the magnitude of underreporting should not vary in persons with or without previous cardiovascular diseases. Because persons who report cocaine use are definite users, the association between cocaine use and MI is probably accurate. Because some of the persons with MI who reported nonuse or did not respond may, in fact, be cocaine users, the magnitude of the association may be undermined. Therefore, the limitations in stratifying the frequency of cocaine use in this study may bias the results toward null.

The methodology used did not permit us to evaluate the likelihood of fatal stroke and MI. Fatal strokes and MI represent less than one third of all cardiovascular disease events.\(^33-36\) However, the exclusion of fatal events may have reduced our ability to detect significant differences, and it is possible that risk factors like cocaine use are more likely to be associated with fatal events. The relationship of cocaine use with subtypes of stroke that are associated with high mortality, such as intracerebral hemorrhage\(^37\) and subarachnoid hemorrhage,\(^38\) cannot be evaluated using the present design. There is a possibility of type II error because of the small number of stroke events observed. If an \(\alpha\) level of 0.05 is assumed with a power of 80%, the present sample size would allow a detection of difference if the stroke event rate was 1.44% in the frequent cocaine users compared with the present rate of 0.35% in nonusers. The OR of 0.5 for the association between cocaine and stroke in our present analysis is very similar to a previous analysis using a case-control design (OR, 0.7).\(^33\) However, the CI of the association in the present analysis (Table 3) includes values of estimated risk of stroke in cocaine or amphetamine users in a previous epidemiological study.\(^24\)

In conclusion, we found that 1 of every 20 persons aged 18 to 45 years reported regular use of cocaine. Regular use was associated with an increased likelihood of nonfatal MI in younger patients. In our analysis, 1 of every 4 nonfatal MIs in young persons was attributable to the frequent use of cocaine in this survey. Behavior modification by public awareness
and education may reduce the cardiovascular morbidity associated with cocaine use.

References
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