Triggering of Myocardial Infarction by Cocaine

Murray A. Mittleman, MD, DrPH; David Mintzer; Malcolm Maclure, ScD; Geoffrey H. Tofler, MB; Jane B. Sherwood, RN; James E. Muller, MD

Background—Cocaine has been implicated as a trigger of acute myocardial infarction in patients with and those without underlying coronary atherosclerosis. However, the magnitude of the increase in risk of acute myocardial infarction immediately after cocaine use remains unknown.

Methods and Results—In the Determinants of Myocardial Infarction Onset Study, we interviewed 3946 patients (1282 women) with acute myocardial infarction an average of 4 days after infarction onset. Data were collected on the use of cocaine and other potential triggers of myocardial infarction. We compared the reported use of cocaine in the hour preceding the onset of myocardial infarction symptoms with its expected frequency by using self-matched control data based on the case-crossover study design. Of the 3946 patients interviewed, 38 (1%) reported cocaine use in the prior year and 9 reported use within the 60 minutes preceding the onset of infarction symptoms. Compared with nonusers, cocaine users were more likely to be male (87% vs 67%, P=0.01), current cigarette smokers (84% vs 32%, P<0.001), younger (44±8 vs 61±13 years, P<0.001), and minority group members (63% vs 11%, P<0.001). The risk of myocardial infarction onset was elevated 23.7 times over baseline (95% CI 8.5 to 66.3) in the 60 minutes after cocaine use. The elevated risk rapidly decreased thereafter.

Conclusions—Cocaine use is associated with a large abrupt and transient increase in the risk of acute myocardial infarction in patients who are otherwise at relatively low risk. This finding suggests that studying the pathophysiological changes produced by cocaine may provide insights into the mechanisms by which myocardial infarction is triggered by other stressors. (Circulation. 1999;99:2737-2741.)

Key Words: cocaine • myocardial infarction • epidemiology

Cocaine has been implicated as a trigger of acute myocardial infarction both in patients free of coronary artery disease and more frequently in patients with underlying coronary atherosclerosis.1–4 Despite these reports, there are no published data from controlled studies evaluating the magnitude of the increase in risk of acute myocardial infarction immediately after cocaine use. With more than 30 million Americans having tried cocaine at least once and a reported 5 million regular users, a better understanding of the magnitude of this cardiac risk is important from a public health perspective.

Although the mechanisms involved in cocaine-induced myocardial infarction are not well understood, it is known that cocaine blocks the presynaptic reuptake of norepinephrine and dopamine, leading to high concentrations of these neurotransmitters at postsynaptic receptor sites.6 This adrenergic stimulation increases myocardial oxygen demand by causing an increase in heart rate, blood pressure, and left ventricular contractility.7 In addition, acute exposure to cocaine has been documented to cause coronary vasoconstriction,8–16 which, together with marked increases in arterial pressure, may lead to disruption of atherosclerotic plaques in the coronary vasculature that are vulnerable to the increase in shear forces.17,18 Furthermore, acute administration of cocaine has been reported to increase platelet aggregability19,20 and may lead to in situ thrombus formation.1,2,4,21–24

To evaluate the magnitude of the risk of having an acute myocardial infarction triggered by the recreational use of cocaine, we collected data on the use of cocaine in 3946 patients (1282 women) with acute myocardial infarction interviewed for the Determinants of Myocardial Infarction Onset Study. In this multicenter, interview-based study, we compared the reported use of cocaine in the hour preceding the onset of myocardial infarction symptoms with its expected frequency by using self-matched control data based on the case-crossover study design.

Methods

Study Population

Between August 1989 and September 1996, a total of 3946 patients (2664 men and 1282 women, age range 20 to 92 years) were interviewed for the Determinants of Myocardial Infarction Onset Study. In this multicenter, interview-based study, we compared the reported use of cocaine in the hour preceding the onset of myocardial infarction symptoms with its expected frequency by using self-matched control data based on the case-crossover study design.
did not significantly differ in any other characteristic (Table 1). The incidence of cocaine use was high (38% vs 6% for nonusers, P = 0.001). We also observed differences in other patient characteristics, including race, age, sex, and BMI. The study population was predominantly male (87% vs 67% for nonusers, P = 0.001).

**Discussion**

These results from the Onset Study corroborate the reports from case-series that cocaine use can trigger the onset of myocardial infarction. However, the confidence intervals for these relative risks are wide, and persistence of a moderately increased risk cannot be ruled out on the basis of these data.

**Table 1. Characteristics of the Study Population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cocaine Use</th>
<th>No Cocaine Use</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>44.1 ± 7.9</td>
<td>6.4 ± 13.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;60</td>
<td>32 (84%)</td>
<td>801 (21%)</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>6 (16%)</td>
<td>1967 (50%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>70+</td>
<td>0 (0%)</td>
<td>1140 (29%)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33 (87%)</td>
<td>2631 (67%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5 (13%)</td>
<td>1277 (33%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Member of a minority group</td>
<td>24 (63%)</td>
<td>430 (11%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>9 (24%)</td>
<td>1031 (26%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Prior angina</td>
<td>9 (24%)</td>
<td>958 (25%)</td>
<td>0.91</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (29%)</td>
<td>1703 (44%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (11%)</td>
<td>740 (19%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Obese*</td>
<td>16 (42%)</td>
<td>1231 (32%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Current smoker</td>
<td>32 (84%)</td>
<td>1262 (32%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medication use before MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>14 (37%)</td>
<td>1394 (36%)</td>
<td>0.88</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>6 (16%)</td>
<td>930 (24%)</td>
<td>0.25</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>4 (11%)</td>
<td>823 (21%)</td>
<td>0.11</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>3 (8%)</td>
<td>507 (13%)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Table 2 shows the distribution of the usual frequency of cocaine use among the 38 patients who reported using cocaine in the year before their myocardial infarction. Of the 38 patients, 9 reported using cocaine within the 60 minutes before the onset of their infarction symptoms. In addition to these 9 patients, 1 patient reported using cocaine between 60 and 120 minutes before the onset of symptoms, and 1 additional patient reported cocaine use in the period from 120 to 180 minutes before myocardial infarction onset.

**Table 2. Usual Frequency of Cocaine Use Among 38 Patients Who Reported Using Cocaine in the Year Before Myocardial Infarction**

<table>
<thead>
<tr>
<th>Usual Frequency of Cocaine Use</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least daily</td>
<td>6 (15.8%)</td>
</tr>
<tr>
<td>≥1/wk and &lt;1/d</td>
<td>12 (31.6%)</td>
</tr>
<tr>
<td>≥1/mo and &lt;1/wk</td>
<td>6 (15.8%)</td>
</tr>
<tr>
<td>&lt;1/mo</td>
<td>14 (36.8%)</td>
</tr>
</tbody>
</table>
and dopamine, leading to a high concentration of these neurotransmitters at postsynaptic receptor sites.6 This adrenergic stimulation in turn leads to an increase in cytosolic Ca\(^{2+}\) concentration in vascular smooth muscle cells. These fluxes in divalent cations may directly contribute to vasoconstriction.41 Third, cocaine has been documented to cause an acute deterioration in left ventricular systolic and diastolic function.44 Pitts et al44 recently demonstrated that an intracoronary infusion of cocaine can lead to an increase in left ventricular end-diastolic pressure and left ventricular end-systolic volume as well as a decrease in left ventricular ejection fraction. A possible mechanism for these effects is that cocaine can alter Ca\(^{2+}\) handling by myocytes. For example, Perreault et al45 demonstrated that cocaine can cause an increase in cytosolic Ca\(^{2+}\) concentration in isolated myocardial tissue. This in turn leads to prolongation of the calcium current and a negative lusitropic effect.45

The present study has several potential limitations. No data were collected on the method of cocaine exposure, for example, intravenous, intranasal, or inhaled crack cocaine use. In addition, because the data are based on patient self-report, some misclassification of exposure probably occurred. For example, patients may be reluctant to report that they had used cocaine before their myocardial infarction. The effect of such a bias would be to reduce the magnitude of the estimated relative risk. In an effort to minimize such reporting bias as well as to maintain patient confidentiality, efforts were made to ensure the patient’s privacy during the interview. Furthermore, to obtain comparable reporting of cocaine use for all of the hourly intervals during the day preceding the infarction, patients were not informed of the duration of the hypothesized hazard period.

There is a possibility of bias caused by differential survival of cases who had a myocardial infarction triggered by different mechanisms. For example, if patients whose infarctions were triggered by cocaine were more likely to die than those whose infarctions were unrelated to cocaine, then the apparent relative risk may be underestimated. On the other hand, it is possible that patients underreport the use of cocaine because of the social stigma attached to it, but they may be relatively accurate about its use on the day of their myocardial infarction because of potential clinical benefit. This may result in an overestimate of the relative risk. One way to control for such recall bias is to use the period from 1 to 3 hours before the infarction as the control period. In this case the null hypothesis is that the 11 episodes of cocaine use would be evenly distributed over the 3 hours
before the onset of myocardial infarction symptoms. What we observed was 9 exposures in the first hour and 1 episode per hour in each of the other 2 hours. This corresponds to a relative risk of 9.0 (95% CI 1.9 to 41.7; P<0.001).

Because of the small number of exposed cases, we were unable to evaluate whether the risk of having a myocardial infarction differed in subsets of patients. For example, on the basis of the work of Moliterno et al, the combination of cocaine use and cigarette smoking might be particularly harmful. Similarly, we were unable to determine whether the risk of sustaining a cocaine-associated myocardial infarction differed for frequent versus infrequent users.

In traditional epidemiological studies of coronary heart disease, confounding by differences in risk factors between individuals is a major threat to validity. A strength of the case-crossover design used in this study is that self-matching ensures that within strata there is no variability in traditional chronic risk factors for coronary heart disease. Thus, by design, confounding by all traditional chronic risk factors for coronary heart disease, whether measured or unmeasured, is controlled for in the analysis.27,31

A limitation of the case-crossover design used in this study is that like case-control studies, the absolute risk of myocardial infarction onset cannot be directly estimated from the data. However, an estimate of the baseline risk can be made with the use of other data sources. For example, on the basis of the Framingham Heart Study risk equation, the baseline risk of acute myocardial infarction for a typical cocaine user in this study (44-year-old male smoker with average levels of other risk factors) is between 1 and 1.5 per million per hour. Thus in the hour after cocaine use, the absolute risk would increase to approximately 30 per million per hour. For a daily user of cocaine, the risk would accumulate over the course of time, leading to an annual excess risk of a coronary heart disease event of approximately 1.5% to 3% per year. Despite the dramatic transient increase in risk after cocaine use, cocaine was a rare trigger of acute myocardial infarction in the Onset Study because of the low prevalence of cocaine use (<1%) in this population.

Previous reports have shown that physical25,29,48 and psychological stress26,49 can trigger the onset of acute myocardial infarction. In this report we have documented pharmacological triggering by showing that cocaine can abruptly increase the risk of acute myocardial infarction in patients who are otherwise at relatively low risk. This finding suggests that studying the pathophysiological changes produced by cocaine may provide insights into the mechanisms by which myocardial infarction is triggered by other stressors. In addition, drug education campaigns ought to include information regarding the magnitude of the cardiac risk associated with cocaine use.

Acknowledgments

This work was supported by grants from the National Heart, Lung, and Blood Institute (HL-41016) and the American Heart Association (9630115N). We are grateful to the Onset Study interviewers for their dedication and Diane Walkoff, BS, for expert assistance in conducting the Onset Study.

References


Triggering of Myocardial Infarction by Cocaine
Murray A. Mittleman, David Mintzer, Malcolm Maclure, Geoffrey H. Tofler, Jane B. Sherwood and James E. Muller

Circulation. 1999;99:2737-2741
doi: 10.1161/01.CIR.99.21.2737

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/99/21/2737

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/