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,5 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.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 at 64 medical centers a median of 4 days after myocardial infarction.

Interviewers identified eligible cases by reviewing coronary care unit admission logs and patients’ charts. For inclusion in the study, patients were required to meet all of the following criteria: at least 1 creatine kinase level above the upper limit of normal for the clinical laboratory performing the test, positive MB isoenzymes, an identifiable onset of pain or other symptoms typical of infarction, and the ability to complete a structured interview. The protocol was approved by the institutional review board at each participating center, and informed consent was obtained from each patient.

Detailed chart reviews and patient interviews were conducted by trained research personnel, as previously described.25,26 Data were collected on standard demographic variables as well as risk factors for coronary artery disease. The interview identified the time, place, and quality of myocardial infarction pain and other symptoms as well as the timing and estimated usual frequency of exposure to potential triggers of myocardial infarction onset during the prior year. In addition, patients were asked if they had used cocaine in the year preceding their infarction. Patients who reported any use of cocaine were also asked to report the last time that they had used cocaine and their usual frequency of using cocaine over the prior year.

**Study Design**

The design of the Onset Study has been described in detail elsewhere.25–29 In brief, we used a case-crossover study design25,27,28 to assess the change in risk of acute myocardial infarction during a brief “hazard period” after exposure to cocaine and other potential triggers of myocardial infarction onset. An important feature of the case-crossover design is that control information for each patient is based on his or her own past exposure experience.23–27,28 Self-matching results in freedom from confounding by risk factors that are stable over time but often differ between study subjects.

Cocaine use in the hazard period, the 1-hour period immediately preceding the onset of myocardial infarction symptoms, was compared with its expected frequency based on control data obtained from the patients. We used the usual frequency of cocaine use over the year prior to myocardial infarction to estimate its expected frequency in an average 1-hour period in this patient population.

**Statistical Analysis**

The analysis of case-crossover data are an application of standard methods for stratified data analysis.27,28,30,31 In this analysis, the stratifying variable is the individual patient, as in a crossover experiment. The ratio of the observed exposure frequency in the hazard period to the expected frequency (from the control information) was used to calculate estimates of the odds ratio as a measure of relative risk.25,27,28 The amount of person-time exposed to cocaine was estimated by multiplying the reported usual annual frequency of exposure by the duration of its hypothesized physiological effect (1 hour). Unexposed person-time was then calculated by subtracting the exposed person-time in hours from the number of hours in 1 year. The data were analyzed with the use of methods for cohort studies with sparse data in each stratum.27,28,32

**Results**

The characteristics of the patients interviewed are presented in Table 1. Of the 3946 patients with myocardial infarction who were interviewed, 38 (1%) reported that they had used cocaine in the year preceding their myocardial infarction. Compared with nonusers, cocaine users were more likely to be male (87% vs 67%, P=0.01), current smokers (84% vs 32%, P<0.001), younger (44±8 vs 61±13 years, P<0.001), and members of a minority group (63% vs 11%, P<0.001).

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.

Within 1 hour after using cocaine, the risk of myocardial infarction onset was elevated 23.7 times (95% CI 8.5 to 66.3). The Figure shows that the relative risk of myocardial infarction was much lower during the second and third hours after cocaine use (controlling for subsequent exposure). These relative risks were not statistically significantly elevated. 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.

**Discussion**

These results from the Onset Study corroborate the reports from case-series that cocaine use can trigger the onset of

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of the Study Population</th>
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<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Mean±SD</td>
</tr>
<tr>
<td>&lt;50</td>
</tr>
<tr>
<td>50–69</td>
</tr>
<tr>
<td>70+</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Member of a minority group</td>
</tr>
<tr>
<td>Medical history</td>
</tr>
<tr>
<td>Prior MI</td>
</tr>
<tr>
<td>Prior angina</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Obese*</td>
</tr>
<tr>
<td>Current smoker</td>
</tr>
<tr>
<td>Medication use before MI</td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td>β-Blockers</td>
</tr>
<tr>
<td>ACE inhibitors</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; ACE, angiotensin-converting enzyme.

*Obesity defined as body mass index >29 kg/m².

**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>
Relative risk of myocardial infarction onset after cocaine use. Relative risk of myocardial infarction onset is plotted on a log-

dynamic stresses; thereafter, hemostatic and vasoconstrictive
tic variables.6 Thus there are several pathways through which

cocaine may trigger cardiovascular events.7 As in our study, the majority of the patients were
to cocaine use and that the elevated risk rapidly decreased thereafter.

The demographics of the cocaine users and the time from
to the time of subsequent cocaine use.

A proposed mechanism for triggering of myocardial infarc-
tion onset when a vulnerable but not necessarily stenotic atherosclerotic plaque disrupts in response to hemo-
dynamic stresses; thereafter, hemostatic and vasoconstrictive
forces determine whether the resultant thrombus becomes
occlusive.5,7,38 Thus there are several pathways through which

cocaine may trigger the onset of acute myocardial infarction.

First, cocaine blocks presynaptic reuptake of norepinephrine
and dopamine, leading to a high concentration of these
neurotransmitters at postsynaptic receptor sites.6 This
adrenergic stimulation in turn causes an increase in heart rate,
blood pressure, and left ventricular contractility.7 Second,
within 15 minutes of intranasal administration of even low
doses of cocaine, coronary vasoconstriction occurs in both
stenotic and nonstenotic segments through stimulation of
α-adrenergic receptors.5,9 In addition, cocaine has been

shown to increase the endothelial release of endothelin,
probably through stimulation of α-receptors.39 Animal mod-

eis indicate that cocaine administration leads to a rapid rise in
intracellular free Ca" and a concomitant loss of intracel-

lular Mg²⁺ in vascular smooth muscle cells. These fluxes
in divalent cations may directly contribute to vasoconstric-
tion.41 Third, cocaine has been documented to cause an
increase in platelet aggregability in vivo and in vitro.
Furthermore, angiographic studies have shown that
some patients who had myocardial infarction after cocaine
use had occlusive thrombi at nonstenotic sites within their
coronary arteries.1,2,4 Finally, accelerated atherosclerosis has
been detected in young cocaine users.4 Although speculative,
it is possible that the development of such subclinical disease
may contribute to the likelihood that a habitual cocaine user
will have vulnerable atherosclerotic plaques present in their
coronary vessels at the time of subsequent cocaine use.

In addition to its effects on coronary arteries, cocaine can
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
jection fraction. A possible mechanism for these effects is
that cocaine may alter Ca²⁺ handling by myocytes. For
example, Perreault et al45 demonstrated that cocaine can
cause an increase in cytosolic Ca²⁺ 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 oc-
curred. 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
hypoththesized 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 infarc-
tions 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 ben-
efit. 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

Relative Risk of MI Onset

<table>
<thead>
<tr>
<th>Hours since cocaine use</th>
<th>0 - 1 hours</th>
<th>1 - 2 hours</th>
<th>2 - 3 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Risk of MI Onset</td>
<td>64</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>95% CI</td>
<td>5.7%</td>
<td>11%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Dashed line represents baseline risk during periods of
nonexposure to cocaine.
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,46,47 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 users 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 stress26–29 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

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