Triggering Myocardial Infarction by Marijuana

Murray A. Mittleman, MD, DrPH; Rebecca A. Lewis; Malcolm Maclure, ScD; Jane B. Sherwood, RN; James E. Muller, MD

Background—Marijuana use in the age group prone to coronary artery disease is higher than it was in the past. Smoking marijuana is known to have hemodynamic consequences, including a dose-dependent increase in heart rate, supine hypertension, and postural hypotension; however, whether it can trigger the onset of myocardial infarction is unknown.

Methods and Results—In the Determinants of Myocardial Infarction Onset Study, we interviewed 3882 patients (1258 women) with acute myocardial infarction an average of 4 days after infarction onset. We used the case-crossover study design to compare the reported use of marijuana in the hour preceding symptoms of myocardial infarction onset to its expected frequency using self-matched control data. Of the 3882 patients, 124 (3.2%) reported smoking marijuana in the prior year, 37 within 24 hours and 9 within 1 hour of myocardial infarction symptoms. Compared with nonusers, marijuana users were more likely to be men (94% versus 67%, \( P < 0.001 \)), current cigarette smokers (68% versus 32%, \( P < 0.001 \)), and obese (43% versus 32%, \( P = 0.008 \)). They were less likely to have a history of angina (12% versus 25%, \( P < 0.001 \)) or hypertension (30% versus 44%, \( P = 0.002 \)). The risk of myocardial infarction onset was elevated 4.8 times over baseline (95% confidence interval, 2.4 to 9.5) in the 60 minutes after marijuana use. The elevated risk rapidly decreased thereafter.

Conclusions—Smoking marijuana is a rare trigger of acute myocardial infarction. Understanding the mechanism through which marijuana causes infarction may provide insight into the triggering of myocardial infarction by this and other, more common stressors. (Circulation. 2001;103:2805-2809.)

Key Words: cannabis ■ myocardial infarction ■ epidemiology ■ cross-over studies

Marijuana is the most widely used illicit drug in the United States. In 1998, >72 million Americans, accounting for 33% of the population older than 12 years, had used marijuana or hashish at least once in their lifetime, with 8.6% reporting using the drug in the past year and 5.0% reporting use in the past month.1 Self-reported use of marijuana is greatest among adults between 18 and 25 years of age.1 Historically, the prevalence of smoking marijuana was very low among older adults. However, as the generation born in the 20 years after the end of the Second World War ages, the prevalence of marijuana use in the age group prone to coronary artery disease has increased.

Marijuana has several well-described effects on the cardiovascular system. For example, smoking marijuana is associated with a dose-dependent increase in the resting heart rate of 20% to 100%.2-10 Blood pressure is typically increased in the supine position,1,3,6,7,9 and postural hypotension, which is often symptomatic, is common. Overall, there is a net increase in myocardial oxygen demand with a decrease in oxygen supply, which is due in part to an increase in carboxyhemoglobin; this results in a lower anginal threshold in patients with chronic stable angina.3,11 Furthermore, there are several reports of myocardial infarction occurring in close proximity to marijuana use in otherwise low-risk individuals.12-14

An Institute of Medicine report on marijuana and medicine released in 1999 noted that although the cardiovascular effects of marijuana do not seem to pose a health problem for healthy young users, they may present a serious problem for older subjects.15 The report also noted that any effect of marijuana use on cardiovascular disease could have a substantial impact on public health. The magnitude of the impact remains to be determined: long-term marijuana users from the late 1960s are now entering the years during which coronary arterial and cerebrovascular diseases become common. The report recommends that “studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which marijuana use is prevalent.”15

To evaluate whether marijuana is a trigger of the onset of an acute myocardial infarction, we collected data on marijuana use in 3882 patients (1258 women) who sustained an
acute myocardial infarction and were interviewed for the Determinants of Myocardial Infarction Onset Study.\textsuperscript{16,17} In this multicenter, interview-based study, we used a case-crossover study design to compare the reported use of marijuana in the hour preceding the onset of myocardial infarction symptoms to its expected frequency using self-matched control data.

**Methods**

**Study Population**

Between August 1989 and September 1996, a total of 3882 patients (2624 men and 1258 women aged 20 to 92 years) were interviewed at 64 medical centers a median of 4 days after their 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 one 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 institutional review board at each participating center approved the protocol, and informed consent was obtained from each patient.

Detailed chart reviews and patient interviews were conducted by research personnel trained as previously described.\textsuperscript{16 –18} Data were collected on standard demographic variables and 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 smoked marijuana in the year preceding their infarction. Patients who reported smoking marijuana were also asked to report the last time that they had smoked marijuana and their usual frequency of smoking marijuana over the prior year. Patients were also asked to report the timing of exposure to marijuana and other potential triggers for each of the 26 hours preceding the onset of their symptoms.

**Study Design**

The design of the Onset Study has been described in detail elsewhere.\textsuperscript{16–21} In brief, we used a case-crossover study design\textsuperscript{16,19,20,22} to assess the change in the risk of acute myocardial infarction during a brief “hazard period” after exposure to marijuana 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.\textsuperscript{16,19,20} Self-matching results in freedom from confounding by risk factors that are stable over time but often differ between study subjects.

Marijuana 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 marijuana use over the year before 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 is an application of standard methods for stratified data analysis.\textsuperscript{19,20,23,24} 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.\textsuperscript{16,19,20} The amount of person-time exposed to marijuana 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 a year. The data were analyzed using methods for cohort studies with sparse data in each stratum.\textsuperscript{19,20,25}

**Sensitivity Analyses**

To evaluate whether exposure to other triggering behaviors could account for the observed effect of smoking marijuana, we conducted a sensitivity analysis excluding patients who smoked marijuana and engaged in other potentially triggering activities in the hour preceding their infarction.

In another sensitivity analysis, we evaluated the timing of marijuana use among the patients who reported smoking it in the 24 hours before the onset of their infarction symptoms. In this analysis, we compared the number of patients who reported smoking marijuana in the hour before symptom onset to the expected number that would arise if smoking marijuana was unrelated to myocardial infarction onset and the frequency of smoking marijuana was evenly distributed over the prior day.

**Results**

The characteristics of the patients interviewed are presented in Table 1. Of the 3882 patients with myocardial infarction who were interviewed, 124 (3.2%) reported that they had smoked marijuana in the year preceding their myocardial infarction. The frequency of smoking marijuana was significantly related to age, with 12.5% of patients younger than 50 years reporting smoking marijuana in the past year. The mean age of users was 44 ± 8 years, compared with 62 ± 13 years for nonusers (P<0.001). Compared with nonusers, patients who smoked marijuana were more likely to be men (94% versus 67%, P<0.001), current cigarette smokers (68% versus 32%,

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Marijuana Users (n = 124)</th>
<th>Marijuana Abstainers (n = 3758)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>43.7 ± 8.0</td>
<td>62.0 ± 12.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;50</td>
<td>96 (77)</td>
<td>672 (18)</td>
<td></td>
</tr>
<tr>
<td>50–69</td>
<td>28 (23)</td>
<td>1952 (52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>70+</td>
<td>0 (0)</td>
<td>1134 (30)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>116 (94)</td>
<td>2508 (67)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8 (6)</td>
<td>1250 (33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Member of a minority group</td>
<td>28 (23)</td>
<td>495 (13)</td>
<td>0.003</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>29 (23)</td>
<td>1038 (28)</td>
<td>0.30</td>
</tr>
<tr>
<td>Prior angina</td>
<td>15 (12)</td>
<td>935 (25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>37 (30)</td>
<td>1659 (44)</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (7)</td>
<td>723 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obese*</td>
<td>53 (43)</td>
<td>1184 (32)</td>
<td>0.008</td>
</tr>
<tr>
<td>Current smoker</td>
<td>84 (68)</td>
<td>1196 (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>43 (35)</td>
<td>1414 (38)</td>
<td>0.51</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>16 (13)</td>
<td>911 (24)</td>
<td>0.004</td>
</tr>
<tr>
<td>ß-blockers</td>
<td>16 (13)</td>
<td>817 (22)</td>
<td>0.02</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>10 (8)</td>
<td>505 (13)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Values are n (%) unless otherwise indicated. MI indicates myocardial infarction; ACE, angiotensin-converting enzyme.

*Obesity was defined as a body mass index >29 kg/m².
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TABLE 2. Usual Frequency of Marijuana Smoking Among 124 Patients Who Reported Using Marijuana in the Year Before Myocardial Infarction

<table>
<thead>
<tr>
<th>Usual Frequency of Smoking Marijuana</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least daily</td>
<td>22 (17.7)</td>
</tr>
<tr>
<td>≥1 per week and &lt;1 per day</td>
<td>30 (24.2)</td>
</tr>
<tr>
<td>≥1 per month and &lt;1 per week</td>
<td>32 (25.8)</td>
</tr>
<tr>
<td>Less than once a month</td>
<td>40 (32.3)</td>
</tr>
</tbody>
</table>


P<0.001), and obese (43% versus 32%, P=0.008). They were less likely to have a history of angina (12% versus 25%, P<0.001) or hypertension (30% versus 44%, P=0.002).

Table 2 shows the distribution of the usual frequency of marijuana use among the 124 patients who reported smoking marijuana in the year before their myocardial infarction. The majority of patients who smoked marijuana reported using it at least once per month (67.7%), with 41.2% smoking marijuana at least weekly.

Of the 124 patients who reported smoking marijuana, 37 reported smoking it within 24 hours of myocardial infarction onset and 9 reported use within 1 hour of myocardial infarction symptom onset. In addition to these 9 patients, 3 patients reported using marijuana between 60 and 120 minutes before the onset of symptoms. Of the 37 patients who reported smoking marijuana within 24 hours of myocardial infarction symptoms, only 5 reported smoking it once per month or less, and 28 (76%) reported smoking it at least weekly. Similarly, 7 of the 9 patients (78%) who reported smoking marijuana within 1 hour of symptom onset reported smoking it at least once per week.

On the basis of a case-crossover analysis that controlled for differences between patients, we found that within 1 hour after smoking marijuana, the risk of myocardial infarction onset was elevated 4.8-fold (95% confidence interval, 2.9 to 9.5; P<0.001) compared with periods of nonuse. In the second hour after smoking, the relative risk was 1.7 (95% confidence interval, 0.6 to 5.1; P=0.34), suggesting a rapid decline in the cardiac effects of marijuana (Figure).

A total of 3 patients who smoked marijuana in the hour before their infarction also engaged in other triggering behaviors that hour. One patient reported using cocaine in addition to smoking marijuana, another reported sexual intercourse, and a third patient reported both sexual intercourse and cocaine use. None of the patients who smoked marijuana in the period 1 to 2 hours before their myocardial infarction reported exposure to other known triggers in that hour. A sensitivity analysis excluding these 3 patients resulted in a relative risk of 3.2 (95% confidence interval, 1.4 to 7.3; P=0.007) for smoking marijuana in the absence of other potential triggers of myocardial infarction.

In another sensitivity analysis, we evaluated the timing of marijuana use among the 37 patients who reported smoking it in the 24 hours before the onset of their infarction symptoms. If smoking marijuana was unrelated to myocardial infarction onset, we would expect these 37 cases to be evenly distributed over the 24-hour period. This sensitivity analysis resulted in a relative risk of 5.8 (95% confidence interval, 2.8 to 12.1).

Because of the small number of exposed cases, we were unable to evaluate whether the risk of having a myocardial infarction associated with smoking marijuana differed in subsets of patients.

Discussion

In the present study, we observed that smoking marijuana was a rare trigger of acute myocardial infarction. The risk of myocardial infarction onset was elevated almost 5-fold in the hour after smoking marijuana and persisted after excluding patients who also engaged in other potentially triggering exposures in that hour. The heightened risk seemed to decline rapidly and was not significantly elevated beyond the first hour. Overall, the use of marijuana among patients in the Onset Study was quite low, consistent with national survey data. Only 3.2% of patients reported smoking marijuana in the year before their infarction. However, among patients younger than 50 years, marijuana smoking was much more common, with 12.5% of patients reporting smoking it.

The elevation in the risk of myocardial infarction in the hour after marijuana use that we observed was much smaller than the risk previously reported for cocaine,17 which unlike marijuana is associated with a marked increase in sympathetic stimulation. We have previously reported that cocaine is associated with a nearly 24-fold increase in the risk of myocardial infarction onset in the hour after use.17

Biological Effects of Marijuana

The effects of cannabinoids are primarily mediated by the activation of cannabinoid receptors, which are present in a variety of tissues including the brain (basal ganglia, substantia nigra pars reticulata, entopeduncular nucleus, globus pallidus, putamen, cerebellum, hippocampus, and cerebral cortex) and cells of the immune system, spleen, blood vessels, and the heart.15,26 The cannabinoid receptors are part of the family of G protein–coupled receptors. Two main subtypes of...
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 using 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 marijuana user in the Framingham Heart Study is between 1 and 1.5 per million per hour. For a daily user of marijuana, the risk would accumulate over the course of time, leading to an annual excess risk of an acute cardiovascular event of 7 per million per hour. For a daily user of marijuana, the risk would accumulate over the course of time, leading to an annual excess risk of an acute cardiovascular event of 7 per million per hour. For a daily user of marijuana, the risk would accumulate over the course of time, leading to an annual excess risk of an acute cardiovascular event of 7 per million per hour.

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References
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