Triggering Myocardial Infarction by Marijuana

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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,[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[3]; 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

Received September 5, 2000; revision received April 2, 2001; accepted April 3, 2001.

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acute myocardial infarction and were interviewed for the Determinants of Myocardial Infarction Onset Study.[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.[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.[16–21] In brief, we used a case-crossover study design[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.[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.[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.[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.[19,20,25]

TABLE 1. Characteristics of the Study Population

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

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

*Obesity was defined as a body mass index >29 kg/m^2.

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 2. Usual Frequency of Marijuana Smoking Among 124 Patients Who Reported Using Marijuana in the Year Before Myocardial Infarction

Usual Frequency of Smoking Marijuana	n (%)
At least daily	22 (17.7)
≥1 per week and <1 per day	30 (24.2)
≥1 per month and <1 per week	32 (25.8)
Less than once a month	40 (32.3)

$P<0.001$), 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%, $P=0.002$).

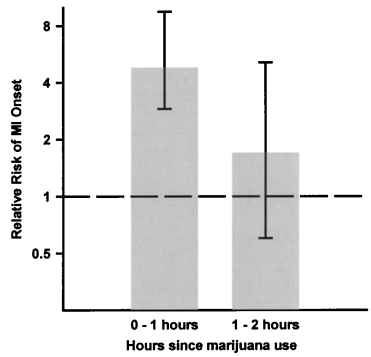
Table 2 shows the distribution of the usual frequency of marijuana use among the 124 patients who reported smoking marijuana in the year before their myocardial infarction. The majority of patients who smoked marijuana reported using it at least once per month (67.7%), with 41.2% smoking marijuana at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



Relative risk of myocardial infarction onset after smoking marijuana. The relative risk of myocardial infarction onset is plotted on a logarithmic scale for each of the 2 hours after smoking marijuana. Relative risks were estimated by comparing the frequency of marijuana use in each of the 2 hours before myocardial infarction onset to its expected frequency on the basis of each patient's reported usual frequency of smoking marijuana over the prior year. Error bars indicate 95% confidence intervals. The dotted line represents the baseline risk during periods with no exposure to marijuana.

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.[1] 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

cannabinoid receptors have been identified and cloned (CB1 and CB2), and a naturally occurring agonist, anandamide, has been identified. In addition to these receptors, Jarai and colleagues[26] recently identified cannabinoid-induced mesenteric vasodilatation through an endothelial site distinct from CB1 or CB2 receptors.

However, the biological effects of smoked marijuana are complex. In addition to the effects of delta-9-tetrahydrocannabinol and other cannabinoids, smoking marijuana is also associated with exposure to particulates and gaseous material arising from the combustion of plant products. In addition, it is not uncommon for marijuana and, more commonly, other cannabinoids such as hashish to be mixed with tobacco.

Several effects of smoked marijuana on the cardiovascular system have been well described. For example, smoking marijuana is associated with a dose-dependent increase in heart rate.[2–10] Although there is much interindividual variability, typical increases in heart rate associated with a single marijuana cigarette range from 20% to 100%, with the peak in heart rate occurring 10 to 30 minutes after beginning to smoke.[2,4,6–8] In addition, most subjects experience an increase in blood pressure, particularly when supine.[3,6,7,9] Postural hypotension after smoking marijuana is not uncommon.[5,9,27] Tolerance to the hemodynamic effects of marijuana can occur with frequent repeated use.[27,28]

In addition to the hemodynamic effects, smoked marijuana is associated with an increase in carboxyhemoglobin, resulting in decreased oxygen-carrying capacity.[3,5,11] Whether marijuana affects the hemostatic balance is unclear. Marijuana may increase factor VII activity; however, there are mixed results in terms of the effects of smoked marijuana on platelet function.[29] Thus, taken together, smoking marijuana is associated with an increase in myocardial oxygen demand and a concomitant decrease in oxygen supply.

Aronow and Cassidy[3,11] demonstrated that among patients with chronic stable angina, the anginal threshold is acutely diminished after smoking a single marijuana cigarette. In particular, the exercise time to angina was decreased by an average of 48% after smoking a single marijuana cigarette, compared with an 8.6% decrease after smoking a marijuana placebo (marijuana cigarette with no delta-9-tetrahydrocannabinol) and a 23% decrease after smoking a high nicotine tobacco cigarette.[3,11]

Thus, some marijuana-associated infarctions may be caused by a myocardial oxygen supply that is inadequate to cope with the increased oxygen demands that occur as result of smoking marijuana. However, the culprit lesion in a majority of myocardial infarctions occurs at the site of a disrupted atherosclerotic plaque.[30,31] A proposed mechanism for the triggering of myocardial infarction is that onset occurs when a vulnerable, but not necessarily stenotic, atherosclerotic plaque is disrupted in response to hemodynamic stresses; thereafter, hemostatic and vasoconstrictive forces determine whether the resultant thrombus becomes occlusive.[32,33] Whether the direct or indirect hemodynamic effects of marijuana are sufficient to cause plaque disruption is speculative, because there are no direct studies of this phenomenon available in the literature.

Limitations

The present study has several potential limitations. Because the data are based on patient self-report, some misclassification of exposure is likely to have occurred. For example, patients may be reluctant to report that they had used marijuana before their myocardial infarction. The effect of such a bias would reduce the magnitude of the estimated relative risk. In an effort to minimize such reporting bias and to maintain patient confidentiality, efforts were made to ensure the patient's privacy during the interview. Furthermore, to obtain comparable reporting of marijuana smoking 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 their myocardial infarction triggered by different mechanisms. For example, if patients whose infarctions were triggered by marijuana were more likely to die than those whose infarctions were unrelated to marijuana, then the apparent relative risk may be underestimated.

However, it is possible that patients under-report long-term use of marijuana 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. However, the sensitivity analysis restricted to the 37 patients who reported smoking marijuana within 24 hours of the onset of myocardial infarction symptoms resulted in a relative risk of 5.8, which is similar to the result based on all patients who reported smoking marijuana in the prior year.

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.[19,24]

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,[34,35] the baseline risk of acute myocardial infarction for a typical marijuana 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 marijuana use, the absolute risk would increase to $\approx$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 $\approx$1.5% to 3% per year. Furthermore, for high-risk patients with either multiple risk factors or established coronary artery disease, the risk may be substantially higher.

In summary, smoking marijuana is a rare trigger of acute myocardial infarction and may pose a health risk to patients with established coronary artery disease and perhaps to individuals with multiple coronary risk factors. Understand-

ing the mechanism by which marijuana causes infarction may provide insight into the triggering of myocardial infarction by this and other, more common stressors.

Acknowledgments

This work was supported by grants from the National Heart, Lung, and Blood Institute (HL41016) and the American Heart Association (9630115N). We are grateful to the Onset Study interviewers for their dedication and to Kate Dwyer, BS, and Diane Walkoff, BS, for their expert assistance in conducting the Onset Study.

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