

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 1999 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/cgi/content/full/99/21/2737>

Subscriptions: Information about subscribing to *Circulation* is online at
<http://circ.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

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 disease¹ 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 aggregability^{19,20} 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

Received October 28, 1998; revision received March 11, 1999; accepted March 23, 1999.

From the Institute for Prevention of Cardiovascular Disease, Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Mass (M.A.M., D.M., G.H.T.); the Department of Epidemiology, Harvard School of Public Health, Boston, Mass (M.A.M., M.M.); the Department of Health and Social Behavior, Harvard School of Public Health, Boston, Mass (J.B.S.); and the Division of Cardiology, Department of Medicine, University of Kentucky Medical Center, Lexington, Ky (J.E.M.).

Correspondence to Murray A. Mittleman, MD, DrPH, Cardiovascular Division, Beth Israel Deaconess Medical Center, 1 Autumn St, Fifth Floor, Boston, MA 02215. E-mail mmittlem@hsph.harvard.edu

© 1999 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>

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 design^{25,27,28} 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.^{25,27,28} 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

TABLE 1. Characteristics of the Study Population

Characteristic	Cocaine Use (n=38)	No Cocaine Use (n=3,908)	P
Age, y			
Mean±SD	44.1±7.9	61.4±13.2	<0.001
<50	32 (84%)	801 (21%)	
50–69	6 (16%)	1967 (50%)	<0.001
70+	0 (0%)	1140 (29%)	
Sex			
Male	33 (87%)	2631 (67%)	
Female	5 (13%)	1277 (33%)	0.01
Member of a minority group	24 (63%)	430 (11%)	<0.001
Medical history			
Prior MI	9 (24%)	1031 (26%)	0.71
Prior angina	9 (24%)	958 (25%)	0.91
Hypertension	11 (29%)	1703 (44%)	0.07
Diabetes mellitus	4 (11%)	740 (19%)	0.19
Obese*	16 (42%)	1231 (32%)	0.16
Current smoker	32 (84%)	1262 (32%)	<0.001
Medication use before MI			
Aspirin	14 (37%)	1394 (36%)	0.88
Calcium channel blockers	6 (16%)	930 (24%)	0.25
β-Blockers	4 (11%)	823 (21%)	0.11
ACE inhibitors	3 (8%)	507 (13%)	0.35

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

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

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.

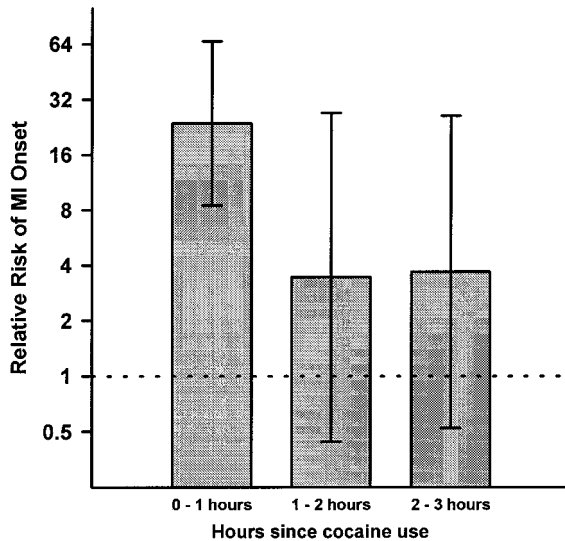
Within 1 hour after using cocaine, the risk of myocardial infarction onset was elevated 23.7 times (95% CI 8.5 to 66.3). The Figure shows that the relative risk of myocardial infarction was much lower during the second and third hours after cocaine use (controlling for subsequent exposure). These relative 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 2. Usual Frequency of Cocaine Use Among 38 Patients Who Reported Using Cocaine in the Year Before Myocardial Infarction

Usual Frequency of Cocaine Use	n (%)
At least daily	6 (15.8%)
≥1/wk and <1/d	12 (31.6%)
≥1/mo and <1/wk	6 (15.8%)
<1/mo	14 (36.8%)



Relative risk of myocardial infarction onset after cocaine use. Relative risk of myocardial infarction onset is plotted on a logarithmic scale for each of the 3 hours after cocaine use. Relative risks were estimated by comparing the frequency of cocaine use in each of the 3 hours before myocardial infarction onset to its expected frequency based on each patient's reported usual frequency of cocaine use over the prior year. Error bars indicate 95% CI. Dotted line represents baseline risk during periods of nonexposure to cocaine.

acute myocardial infarction.^{1,2,4,33} We found that users of cocaine sustained a transient 24-fold increase in risk of myocardial infarction in the hour immediately after cocaine use and that the elevated risk rapidly decreased thereafter.

The demographics of the cocaine users and the time from cocaine use to onset of infarction symptoms in our study population was similar to that seen in other reports of cocaine-induced chest pain and infarction.^{2,34-36} For example, Hollander et al³⁴ reported on 246 patients admitted to the emergency departments of 6 municipal hospitals with chest pain after cocaine use. In this population, of whom only 14 (5.7%) had a documented myocardial infarction, the median interval between cocaine use and onset of chest pain was 60 minutes. As in our study, the majority of the patients were regular cocaine users who were young, male, smokers, and members of minority groups.

A proposed mechanism for triggering of myocardial infarction is that onset occurs when a vulnerable but not necessarily stenotic atherosclerotic plaque disrupts in response to hemodynamic stresses; thereafter, hemostatic and vasoconstrictive forces determine whether the resultant thrombus becomes occlusive.^{37,38} 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.^{8,9} In addition, cocaine has been

shown to increase the endothelial release of endothelin, probably through stimulation of σ -receptors.³⁹ Animal models indicate that cocaine administration leads to a rapid rise in intracellular free Ca^{2+} ^{40,41} and a concomitant loss of intracellular Mg^{2+} ^{42,43} in vascular smooth muscle cells. These fluxes in divalent cations may directly contribute to vasoconstriction.⁴¹ Third, cocaine has been documented to cause an increase in platelet aggregability in *in vivo*²⁰ and *in vitro* testing.¹⁹ 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 ejection fraction. A possible mechanism for these effects is that cocaine may 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,⁸ 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 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 physical^{25,29,48} and psychological stress^{26,49} 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

- Minor RL Jr, Scott BD, Brown DD, Winniford MD. Cocaine-induced myocardial infarction in patients with normal coronary arteries. *Ann Intern Med.* 1991;115:797–806.
- Smith HW III, Liberman HA, Brody SL, Battey LL, Donohue BC, Morris DC. Acute myocardial infarction temporally related to cocaine use. Clinical, angiographic, and pathophysiologic observations. *Ann Intern Med.* 1987;107:13–18.
- Williams MJ, Stewart RA. Serial angiography in cocaine-induced myocardial infarction. *Chest.* 1997;111:822–824.
- Hollander JE, Hoffman RS. Cocaine-induced myocardial infarction: an analysis and review of the literature. *J Emerg Med.* 1992;10:169–177.
- Annual Data 1987. Data from the Drug Abuse Warning Network. Series 1, No. 7 of National Institute on Drug Abuse series. 1988. Rockville, Md: National Institute on Drug Abuse; 1988.
- Ritchie JM, Greene NM. Local anesthetics. In: Gilman AG, Rall TW, Nies AS, Taylor P, eds. *Goodman and Gilman's The Pharmacologic Basis of Therapeutics.* New York, NY: Pergamon Press; 1990:311–331.
- Boehrer JD, Moliterno DJ, Willard JE, Snyder RW II, Horton RP, Glamann DB, Lange RA, Hillis LD. Hemodynamic effects of intranasal cocaine in humans. *J Am Coll Cardiol.* 1992;20:90–93.
- Moliterno DJ, Willard JE, Lange RA, Negus BH, Boehrer JD, Glamann DB, Rossen JD, Winniford MD, Hillis LD. Coronary-artery vasoconstriction induced by cocaine, cigarette smoking, or both. *N Engl J Med.* 1994;330:454–459.
- Lange RA, Cigarroa RG, Yancy CW Jr, Willard JE, Popma JJ, Sills MN, McBride W, Kim AS, Hillis LD. Cocaine-induced coronary-artery vasoconstriction. *N Engl J Med.* 1989;321:1557–1562.
- Lange RA, Cigarroa RG, Flores ED, McBride W, Kim AS, Wells PJ, Bedotto JB, Danziger RS, Hillis LD. Potentiation of cocaine-induced coronary vasoconstriction by beta-adrenergic blockade. *Ann Intern Med.* 1990;112:897–903.
- Nademanee K, Gorelick DA, Josephson MA, Ryan MA, Wilkins JN, Robertson HA, Mody FV, Intarachot V. Myocardial ischemia during cocaine withdrawal. *Ann Intern Med.* 1989;111:876–880.
- Zimmerman FH, Gustafson GM, Kemp HG Jr. Recurrent myocardial infarction associated with cocaine abuse in a young man with normal coronary arteries: evidence for coronary artery spasm culminating in thrombosis. *J Am Coll Cardiol.* 1987;9:964–968.
- Ascher EK, Stauffer JC, Gaasch WH. Coronary artery spasm, cardiac arrest, transient electrocardiographic Q waves and stunned myocardium in cocaine-associated acute myocardial infarction. *Am J Cardiol.* 1988; 61:939–941.
- Flores ED, Lange RA, Cigarroa RG, Hillis LD. Effect of cocaine on coronary artery dimensions in atherosclerotic coronary artery disease: enhanced vasoconstriction at sites of significant stenoses. *J Am Coll Cardiol.* 1990;16:74–79.
- Brogan WC III, Lange RA, Glamann DB, Hillis LD. Recurrent coronary vasoconstriction caused by intranasal cocaine: possible role for metabolites. *Ann Intern Med.* 1992;116:556–561.
- Brogan WC III, Lange RA, Kim AS, Moliterno DJ, Hillis LD. Alleviation of cocaine-induced coronary vasoconstriction by nitroglycerin. *J Am Coll Cardiol.* 1991;18:581–586.
- Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (1). *N Engl J Med.* 1992;326:242–250.
- Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (2). *N Engl J Med.* 1992;326:310–318.
- Togna G, Tempesta E, Togna AR, Dolci N, Cebo B, Caprino L. Platelet responsiveness and biosynthesis of thromboxane and prostacyclin in response to in vitro cocaine treatment. *Haemostasis.* 1985;15:100–107.
- Kugelmass AD, Shannon RP, Yeo EL, Ware JA. Intravenous cocaine induces platelet activation in the conscious dog. *Circulation.* 1995;91: 1336–1340.
- Haines JD Jr, Sexter S. Acute myocardial infarction associated with cocaine abuse. *South Med J.* 1987;80:1326–1327.
- Hadjimiltiades S, Covalesky V, Manno BV, Haaz WS, Mintz GS. Coronary arteriographic findings in cocaine abuse-induced myocardial infarction. *Cathet Cardiovasc Diagn.* 1988;14:33–36.
- Kossowsky WA, Lyon AF. Cocaine and acute myocardial infarction: a probable connection. *Chest.* 1984;86:729–731.
- Lee HO, Eisenberg MJ, Drew D, Schiller NB. Intraventricular thrombus after cocaine-induced myocardial infarction. *Am Heart J.* 1995;129: 403–405.
- Mittleman MA, Maclure M, Tofler GH, Sherwood JB, Goldberg RJ, Muller JE, for the Determinants of Myocardial Infarction Onset Study Investigators. Triggering of acute myocardial infarction by heavy

- exertion: protection against triggering by regular exertion. *N Engl J Med*. 1993;329:1677–1683.
26. Mittleman MA, Maclure M, Sherwood JB, Mulry RP, Tofler GH, Jacobs SC, Friedman R, Benson H, Muller JE. Triggering of myocardial infarction by episodes of anger. *Circulation*. 1995;92:1720–1725.
 27. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol*. 1991;133:144–153.
 28. Mittleman MA, Maclure M, Robins JM. Control sampling strategies for case-crossover studies: an assessment of relative efficiency. *Am J Epidemiol*. 1995;142:91–98.
 29. Muller JE, Mittleman MA, Maclure M, Sherwood JB, Tofler GH. Triggering myocardial infarction by sexual activity: low absolute risk and prevention by regular exertion. *JAMA*. 1996;275:1405–1409.
 30. Rothman KJ. *Modern Epidemiology*. Boston, Mass: Little, Brown & Co; 1986.
 31. Wacholder S, Silverman DT, McLaughlin JK, Mandel JS. Selection of controls in case-control studies. *Am J Epidemiol*. 1992;135:1019–1028.
 32. Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. *Biometrics*. 1985;41:55–68.
 33. Moliterno DJ, Lange RA, Gerard RD, Willard JE, Lackner C, Hillis LD. Influence of intranasal cocaine on plasma constituents associated with endogenous thrombosis and thrombolysis. *Am J Med*. 1994;96:492–496.
 34. Hollander JE, Hoffman RS, Gennis P, Fairweather P, DiSano MJ, Schumb DA, Feldman JA, Fish SS, Dyer S, Wax P, Whelan C, Schwartzwald E. Prospective multicenter evaluation of cocaine-associated chest pain: Cocaine Associated Chest Pain (COCHPA) Study Group. *Acad Emerg Med*. 1994;1:330–339.
 35. Hollander JE, Todd KH, Green G, Heilpern KL, Karras DJ, Singer AJ, Brogan GX, Funk JP, Strahan JB. Chest pain associated with cocaine: an assessment of prevalence in suburban and urban emergency departments. *Ann Emerg Med*. 1995;26:671–676.
 36. Amin M, Gabelman G, Karpel J, Buttrick P. Acute myocardial infarction and chest pain syndromes after cocaine use. *Am J Cardiol*. 1990;66:1434–1437.
 37. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. *Circulation*. 1989;79:733–743.
 38. Muller JE, Abela GS, Nesto RW, Tofler GH. Triggers, acute risk factors and vulnerable plaques: the lexicon of a new frontier. *J Am Coll Cardiol*. 1994;23:809–813.
 39. Wilbert-Lampen U, Seliger C, Zilker T, Arendt RM. Cocaine increases the endothelial release of immunoreactive endothelin and its concentration in human plasma and urine: reversal by coincubation with σ -receptor antagonists. *Circulation*. 1998;98:385–390.
 40. Zhang A, Cheng TP, Altura BT, Altura BM. Acute cocaine results in rapid rises in intracellular free calcium concentration in canine cerebral vascular smooth muscle cells: possible relation to etiology of stroke. *Neurosci Lett*. 1996;215:57–59.
 41. He GQ, Zhang A, Altura BT, Altura BM. Cocaine-induced cerebrovasospasm and its possible mechanism of action. *J Pharmacol Exp Ther*. 1994;268:1532–1539.
 42. Altura BM, Zhang A, Cheng TP, Altura BT. Cocaine induces rapid loss of intracellular free Mg^{2+} in cerebral vascular smooth muscle cells. *Eur J Pharmacol*. 1993;246:299–301.
 43. Huang QF, Gebrewold A, Altura BT, Altura BM. Cocaine-induced cerebral vascular damage can be ameliorated by Mg^{2+} in rat brain. *Neurosci Lett*. 1990;109:113–116.
 44. Pitts WR, Vongpatanasin W, Cigarroa JE, Hillis LD, Lange RA. Effects of the intracoronary infusion of cocaine on left ventricular systolic and diastolic function in humans. *Circulation*. 1998;97:1270–1273.
 45. Perreault CL, Hague NL, Ransil BJ, Morgan JP. The effects of cocaine on intracellular Ca^{2+} handling and myofilament Ca^{2+} responsiveness of ferret ventricular myocardium. *Br J Pharmacol*. 1990;101:679–685.
 46. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J*. 1993;121:293–298.
 47. Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile: a statement for health professionals: American Heart Association Scientific Statement. *Circulation*. 1991;83:356–362.
 48. Willich SN, Lewis M, Lowel H, Arntz H-R, Schubert F, Schroder R, for the Triggers and Mechanisms of Myocardial Infarction Study Group. Physical exertion as a trigger of acute myocardial infarction. *N Engl J Med*. 1993;329:1684–1690.
 49. Mittleman MA, Maclure M, Nachnani M, Sherwood JB, Muller JE. Educational attainment, anger, and the risk of triggering myocardial infarction onset: the Determinants of Myocardial Infarction Onset Study Investigators. *Arch Intern Med*. 1997;157:769–775.