Clinical Investigation

Smoking Is a Risk Factor for Coronary Spasm in Young Women

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Background. Risk factors for pure coronary spasm are not known. Clinical observations have pointed to cigarette smoking, a known risk factor for obstructive coronary artery disease.

Methods and Results. We conducted a case–neighborhood control study of premenopausal women, a population segment with the lowest prevalence of obstructive coronary artery disease. The cases were 21 premenopausal women (age range, 36–41 years) with angiographically proven coronary spasm. All coronary arteriograms were analyzed by two independent experienced cardiologists on two occasions. There were no differences between analyses; all cases had normal baseline coronary angiogram except for two, who had less than 20% coronary luminal stenosis in segments other than the site of the focal vasospasm. All cases had normal hemodynamics at rest, normal left ventricular function, and were in sinus rhythm. Ascertainment of the cases was done by angiographic demonstration of focal coronary spasm spontaneously or by ergonovine provocation. Six cases developed spontaneous coronary spasm before catheter engagement, and in 15, coronary spasm was induced by ergonovine provocation. Each case was asked to name as many as possible female neighborhood acquaintances of similar age and racial background who were willing to answer the same standardized questionnaire. The same standardized questionnaire was completed for each case and each control (n=63). The standardized questionnaire was designed to obtain information on health characteristics, habits, socioeconomic status, and education. Only cigarette smoking was significantly more prevalent among coronary spasm cases. Cigarette smokers were 13 cases (62%) and 11 controls (17.5%) (p<0.001). The odds ratio was 7.7, with a 95% confidence interval of 2.6–23.1.

Conclusions. These findings suggest that there is a very strong association between cigarette smoking and pure coronary spasm in young women. (Circulation 1992;85:905–909)

Key Words • coronary spasm • cigarette smoking • premenopausal women

Although considerable research has been done for more than a decade on spontaneous coronary spasm¹ and its effective albeit costly therapy,² the causes of and predisposing factors for coronary vasospasm remain unknown. In an effort to identify risk factors for spontaneous coronary spasm by using prospectively collected clinical observations, we tested the hypothesis that there is an association between cigarette smoking and focal coronary spasm. Because coronary spasm frequently coexists with obstructive coronary artery disease,⁶ we conducted a case–control study of young women, a population segment with the lowest prevalence of obstructive coronary artery disease.

Methods

One hundred fourteen consecutive premenopausal women were referred by their attending physicians to the cardiac catheterization laboratories of the St. Louis University Medical Center (St. Louis, Mo.) and the Evangelismos and Hyghia Hospitals (Athens, Greece) between July 1983 and June 1988 for evaluation of rest angina. Premenopausal state was reported by the referring physicians and confirmed by direct patient interview. Informed consent was obtained from each patient before cardiac catheterization and ergonovine provocation testing.⁷ Coronary angiography was performed in the fasting state. No patient had smoked or taken sublingual nitrates for at least 8 hours before cardiac catheterization. All antianginal medications were discontinued 24 hours before cardiac catheterization. Coronary angiography was performed by the Judkins technique. Fifty-nine patients had normal hemodynamics, normal coronary angiogram, and negative ergonovine provocation test⁷; their episodes of chest pain at rest were attributed to extracardiac causes, to mitral valve prolapse, or to syndrome X. Fifteen patients had normal hemodynamics and a normal coronary angiogram, but the ergonovine provocation test⁷ was not done. Nineteen patients had angiographically significant coronary artery disease with luminal stenosis of at least 75% of one or more coronary arterial branches, and ergonovine was not administered.

Twenty-one premenopausal women with angina who had normal baseline hemodynamics and normal coronary angiogram developed coronary spasm either spontaneously in the cardiac catheterization laboratory or...
after ergonovine provocation.7 These 21 patients are the cases of this case–neighborhood control study.

Cases

Twenty-one premenopausal women (mean age, 39.5 years; range, 36–44 years) with coronary spasm were studied in the cardiac catheterization laboratories of the Evangelismos and Hgyia Hospitals (n = 8) and the St. Louis University Medical Center (n = 13). The patients (cases) were referred for evaluation of angina pectoris occurring most frequently at rest (n = 18) and both at rest and with exercise (n = 3). The patients were evaluated before coronary angiography with standard 12-lead ECGs at rest and during angina or anginalike symptoms, with continuous ECG recordings (Holter monitor recordings) and 201Tl myocardial imaging.8 Ascertainment of the cases was done by coronary angiography performed before, during, and after ergonovine provocation.7 The noninvasive evaluation that preceded coronary angiography revealed ST elevation on the 12-lead or the continuous ECG monitoring in 13 cases, reversible ischemia on 201Tl myocardial imaging during nonangiographic ergonovine testing in four, and extensive areas of reversible defects (ischemia) on exercise 201Tl myocardial imaging without concomitant ischemic ECG changes in one. Three cases had no recorded evidence for transient myocardial ischemia detected by noninvasive diagnostic methods before coronary arteriography and ergonovine provocation. All cases except one had ST-segment elevation of more than 1 mm on ECG during angiographic appearance of coronary spasm.8 One patient had nondiagnostic ischemic ST changes; she was evaluated for exertional angina and exertional syncope. During exercise 201Tl scintigraphy, this patient developed marked reversible defects anterolaterally and inferiorly on the planar images8 without diagnostic ECG changes; before the administration of ergonovine, she developed spasm of the main left and right coronary arteries.9 Ergonovine provocation was administered intravenously in three successive doses (0.02, 0.10, and 0.28 mg) to induce coronary spasm. A temporary standby cardiac pacemaker was inserted via the femoral vein before the administration of ergonovine. Twelve-lead ECGs were recorded every 3 minutes. Coronary spasm was promptly reversed by intracoronary nitroglycerin in all cases. During coronary angiography, efforts were made to duplicate rotation and skew angles, height, and magnification factors of the x-ray image intensifier so that comparable arteriograms were obtained before, during, and after spontaneous or provoked spasm.

All coronary arteriograms were analyzed by two independent experienced cardiologists on two occasions. There was no significant difference between analyses. All cases had angiographically normal baseline coronary angiogram except for two, who had less than 20% coronary spasm; all had normal hemodynamics at rest and normal ventricular function and were in sinus rhythm.

Ascertainment of the cases was done by angiographic demonstration of focal coronary spasm spontaneously or by ergonovine provocation. Six cases developed spontaneous coronary spasm before catheter engagement, and in 15, coronary spasm was induced by ergonovine provocation.

A standardized questionnaire was completed for each case and each control by one of the authors (D.G.C.). The following specific information was obtained from each case and control individual: educational status, marital status, occupational history, religious preference, place of birth, state of health, medical history, family history with special emphasis on cardiovascular disease and sudden death, body height, fluctuations of body weight, menstrual pattern, parity, age during pregnancies, complications during pregnancies, miscarriages and abortions, known high blood pressure, diabetes mellitus, known hyperlipidemia, migraine headaches, nonmigrainous headaches, bronchial asthma, cold-mediated peripheral vasospasm manifested as Raynaud’s symptoms, known allergies, use of oral contraceptives, use of recreational drugs (marijuana, cocaine, etc.), self-reported history of alcohol use and abuse, physical exercise, and athletic activities. Under the subtitle “History of Tobacco Use,” the following questions were asked: 1) Have you ever smoked cigarettes? 2) Do you currently smoke (at the time of the angiographic diagnosis of coronary spasm for cases)? 3) What is the number of cigarettes smoked per day? 4) What is the number of years of smoking? 5) What is the number of years stopped? 6) Do you have a history of smoking cigars or a pipe?

Controls

Each case was asked to name as many as possible female neighborhood acquaintances of similar age and racial background who were willing to answer the same standardized questionnaire. No neighborhood acquaintance or friend who was willing to answer the questionnaire was excluded.

The purpose of the study was explained to each control. All controls were interviewed separately, and consent to participate in this study was obtained. The standardized questionnaire used for both cases and controls was designed to obtain information on health characteristics, habits, and socioeconomic factors. Each case and the corresponding matched controls were regarded as a separate subgroup. Two cases had difficulty in identifying neighborhood controls and were asked to recommend friends as controls. The information from each questionnaire was abstracted onto study forms and handled with confidentiality.

Statistical Analysis

A χ2 analysis (with Yates’ correction for fewer than five observations) was performed to compare cases with controls. A two-tailed probability value of <0.05 was considered statistically significant. A simple odds ratio and its corresponding 95% confidence interval were estimated10 for the relation of coronary spasm and smoking.

Results

Nineteen cases were matched with 57 neighborhood controls, and two cases were matched with six female friends who served as controls (Table 1). The controls were apparently healthy women with no known chronic illnesses or medical problems and no historical or current evidence for angina pectoris or atypical chest pain syndromes. Overall controls were of similar age
TABLE 1. Characteristics of Cases and Controls in Study of Premenopausal Women With Coronary Vasospasm

|                          | Cases (n=21) (39.5±3.6 years old) | Controls (n=63) (38.5±2.5 years old) | p  
|--------------------------|-----------------------------------|--------------------------------------|-----
|                         | n      | %     | n      | %     |     |
| ≥12 Years of schooling   | 21     | 100   | 63     | 100   | NS  |
| Ever married             | 20     | 95    | 60     | 95    | NS  |
| Negative medical history | 15     | 71    | 52     | 83    | NS  |
| Family history of CVD    | 7      | 33    | 20     | 32    | NS  |
| Parity                   |        |       |        |       |     |
| Nulliparous              | 3      | 14    | 8      | 13    | NS  |
| Low parity (1–3 live births) | 14    | 67    | 44     | 70    | NS  |
| High parity (>3 live births) | 4    | 19    | 11     | 17.5  | NS  |
| Known diabetes mellitus  | 0      | 0     | 0      | 0     |     |
| Known high blood pressure| 3      | 14    | 7      | 11    | NS  |
| Migraine headaches       | 7      | 33    | 10     | 16    | NS  |
| History of bronchial asthma | 5    | 24    | 11     | 17.5  | NS  |
| Peripheral vasospasm     |        |       |        |       |     |
| (manifested as Raynaud's symptoms) | 2    | 9.5   | 1      | 1.6   | NS  |
| Use of oral contraceptives| 8      | 38    | 22     | 35    | NS  |
| Self-reported use of alcohol (socially) | 16  | 76    | 41     | 65    | NS  |
| Self-reported alcohol abuse | 0   | 0     | 1      | 1.6   | NS  |
| Smokers (see Table 2)    | 13     | 62    | 11     | 17.5  | <0.001 |

(mean age; 38.5 years; range, 35–46 years) to cases and compared well regarding race, marital status, socioeconomic status, years of schooling, occupational history, religious preference, place of birth, medical history, family history, body weight and body weight changes, height, parity, menstrual history, known hyperlipidemia, known diabetes mellitus, known high blood pressure, use of birth control pills past and present, no history of recreational drug use, self-reported alcohol use, and self-reported alcohol abuse (Table 1). The narrow age range of both cases (36–44 years) and controls (35–46 years) does not allow a meaningful distribution analysis by age stratification. Among the cases, there were 20 Caucasian women and one black woman; among the controls, there were 60 Caucasian and three black women.

Two variables occurred more frequently among the cases: headaches and cigarette smoking. Migraine headaches were reported by seven cases (33%) and by 10 controls (16%) (p=0.16). Thirteen cases (62%) and 11 controls (17.5%) (p<0.001) were cigarette smokers. Four of the cases had migraine headaches and were smokers, and three controls described attacks of migraine headaches and were smokers. Although one third of the cases reported migraine headaches and four of the seven were smokers, the sample size is too small to provide an answer to the question of whether smokers with migraine headaches and Raynaud’s phenomenon are more likely to develop coronary spasm than women with migraine headaches and Raynaud’s alone. There were three individuals who reported symptoms of peripheral vasospasm: two cases and one control. Regarding oral contraceptive use, the percentage is similar between cases and controls. The history of cigarette smoking among cases and controls is summarized in Table 2. Smoking was similarly associated with coronary spasm in both metropolitan areas. All cases were referred by their attending physicians to cardiac catheterization for evaluation of frequent episodes of angina at rest and not because of their smoking habits. At the time of the referral, smoking was not suspected to be associated with the patient’s symptoms or angiographic findings. The reference category for the estimation of the odds ratio is for nonsmokers; all cases were current smokers at the time of the angiographic diagnosis. The odds ratio of cigarette smoking and coronary spasm was 7.7, with a 95% confidence interval of 2.6–23.1. No study participant had ever smoked cigars regularly; one control woman was an infrequent pipe smoker. All study participants reported infrequent use of small quantities of wine or beer.

All cases were using prescribed medications after seeking medical attention for their symptomatology. Use of oral contraceptives, peripheral vasospasm, and bronchial asthma had an equally low prevalence among cases and controls. There was no difference in percentage with a positive family history of cardiovascular disease between cases and controls.

Discussion

This study demonstrates a strong association between cigarette smoking and coronary spasm among premenopausal women. The sample size is small. Intravenous ergonovine provocation test has been used in the cardiac catheterization laboratory to document spasm of the epicardial coronary arteries in syndromes associated with chest symptoms and ECG changes occurring simultaneously. There may be a potential bias in the selection of controls. We did not use hospitalized controls because they may differ from healthy individuals in a number of ways, including vascular disease. Neither cases nor controls were aware of the hypothesis tested. There was no selection bias on the part of the investi-
gators in that no premenopausal control woman was excluded. There were no significant cultural differences regarding smoking among women of the St. Louis metropolitan area and the Athens metropolitan area. Friends serving as controls may have resulted in over-matching with respect to potential risk factors. No control individual had angina pectoris or atypical chest pain syndrome at any time. Premenopausal women were chosen as the study population because this group probably has a higher prevalence of coronary vasospasm in the absence of obstructive coronary artery disease. The diagnosis of "pure" coronary spasm was established by the demonstration of angiographically normal coronary arteries before and after spontaneous or provoked coronary spasm.

A potential selection bias in referral to coronary angiography may exist. Physicians have been categorized as interventionists or oriented toward health maintenance.11 Personal characteristics of the physician, such as age and education,12,13 could have potentially influenced the clinician’s decision to refer young women to coronary angiography. The colleague-dependent consultant responds to pressure from the referring physicians to make a definitive diagnosis. The personality of both the physician and the patient may have an independent influence on the decision to have coronary angiography performed. A number of female patients with chest pain syndromes carry the diagnosis of coronary spasm without angiographic confirmation. The patients of the present study were all white except for one. They all had at least 12 years of schooling and resided in middle- to upper-income neighborhoods. White patients undergo one third more14 to one half more15 coronary angiography in the United States. In the Coronary Artery Surgery Study,16 which examined patterns of care for a group of patients who underwent angiography, whites preferred a more technological approach. Access, ability to pay, payer, and median income by neighborhood (zip code) play a significant role in the procedure used.14 Patients from lower socio-cultural classes are less likely to seek care or to use health services even when they are available.17 Income was found to have a strong positive effect on hospital-based procedures, although the association was less strong in 1970 than in 1963.18 Rates for coronary angiography have been increasing since 1979.19 In this study, premenopausal women were referred to coronary angiography for further evaluation of chest pain occurring primarily at rest; smoking habit did not appear to be a factor in the decision to perform coronary angiography. This is not a population-based study; hence, we did not assess the prevalence of smoking among women with chest pain or anginalike symptoms who were not admitted to the hospital.

In this as in other case-control studies, the selection of an appropriate comparison group is of critical importance. Our controls were selected to represent a population of women who would have been identified and included as cases had they also developed coronary spasm. Studies using hospitalized and nonhospitalized controls have demonstrated that as a group, hospitalized patients are more likely to smoke cigarettes20 and be heavy alcohol drinkers21 than nonhospitalized individuals. The result of using hospital controls for study of any of these risk factors could be a biased estimate of effect.22 The use of general population controls assures the greatest level of comparability because they come from the same source of population that gave rise to the cases. However, the quality of the information may differ between cases and controls because those of the general population may not recall exposures with the same level of accuracy as those who have developed the disease.22 Neighbors as controls share the advantage of general population controls in that they are healthy but are more likely to be cooperative than members of the general population because of an interest in the case. They may also offer a degree of control of important confounding factors related to ethnic background, socioeconomic status, and an environment that is not otherwise easily achieved. Family members and friends as controls are more likely to be similar to the cases, and an underestimate of the true effect of the exposure under investigation may result. Family and friends are less suitable controls in studies of factors such as diet or smoking because individuals who are closely associated are likely to have similar exposure.23 The prevalence of smoking in the control group is lower than in the general population,24 but the difference is small when taking socioeconomic, especially educational factors, into consideration.24 All controls had at least 12 years of schooling. The odds ratio for smoking applied to premenopausal population calculated here may be overestimated.

It would be of interest to know whether smoking is more likely to induce coronary spasm in women with other signs of vascular reactivity. Are women with migraine headaches and Raynaud’s who smoke more likely to suffer coronary spasm than women with migraine headaches and Raynaud’s alone? And is there an interaction of smoking with oral contraceptive use? A bigger sample than this study provides may give the answers to these important questions.

Table 2. History of Cigarette Smoking in Premenopausal Women With Coronary Vasospasm

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<th>Cases (n=21)</th>
<th>Controls (n=63)</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
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<tr>
<td>Never smoked</td>
<td>8</td>
<td>38</td>
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<tr>
<td>Current smokers*</td>
<td>13</td>
<td>62</td>
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<tr>
<td>&lt;1 PPD</td>
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<td>1</td>
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<td>31</td>
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<td>39</td>
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<td>&gt;2</td>
<td>4</td>
<td>31</td>
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<td>Years of smoking</td>
<td>Mean</td>
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<td>Ex-smokers</td>
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<tr>
<td>Years stopped</td>
<td>Mean, 11 (range, 0.5-20)</td>
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</table>

PPD, packs of cigarettes smoked per day.

*Current at time of angiographic diagnosis of coronary spasm for cases.
It is possible that spontaneous coronary spasm results from a local exaggerated constrictor response to a generalized stimulus.\textsuperscript{22} Spontaneous focal coronary spasm may result from the interaction between local coronary hyperactivity and a generalized stimulus that affects all coronary arteries. Cigarette smoking can cause silent ischemic disturbances of coronary flow\textsuperscript{26} mediated by vasocostriction. In women, smoking has been associated with increased risk for coronary heart disease,\textsuperscript{27} increased risk of nonfatal myocardial infarction,\textsuperscript{28} and increased cardiovascular mortality.\textsuperscript{29} Coronary spasm can cause both myocardial infarction\textsuperscript{30} and sudden death from asystolic or ventricular tachycardia.\textsuperscript{31}

There has been a smaller decline in the prevalence of smoking among women than men.\textsuperscript{32} Smoking cessation studies suggest that pathophysiological factors such as hypoxemia, increased oxygen demand, nicotine effect on vascular tone, and the effects of carbon monoxide on oxygen delivery may be responsible for the excess coronary mortality because among ex-smokers there is a reduction of coronary mortality risk similar to that of never-smokers.\textsuperscript{33} One of these reversible factors may well be coronary spasm and resultant myocardial ischemia triggering lethal cardiac arrhythmias. The results of this study show a very strong association between cigarette smoking and coronary spasm in premenopausal women. Strong antismoking warnings should be given to all smokers with known or suspected coronary artery spasm.

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