Cigarette Smoking Is a Major Risk Factor for Coronary Spasm

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Background. Although there have been many studies on the risk factors for coronary artery disease, the etiology of coronary artery spasm has not yet been determined.

Methods and Results. After diagnosis by coronary arteriography, various risk factors were compared between two groups of subjects using logistic regression analysis. The vasospasm group included 175 patients with angiographically determined coronary artery spasm but no coronary artery narrowing exceeding 25% of the luminal diameter. The control group comprised 176 subjects with completely normal coronary arteries and a negative response to ergonovine maleate. The adjusted odds ratio and 95% confidence interval for smoking as a risk factor for vasospasm was 2.41 and 1.53–3.82, respectively (p < 0.05). The adjusted odds ratios for total cholesterol, low density lipoprotein, high density lipoprotein, triglycerides, diabetes mellitus, and body mass index, calculated by multivariate logistic regression analysis, were not statistically nonsignificant.

Conclusions. Smoking appears to be a major risk factor for vasospastic angina without significant coronary narrowing. The other risk factors for coronary artery disease may not contribute to coronary vasospasm. (Circulation 1993;87:76–79)

KEY WORDS • coronary artery spasm • atherosclerosis, coronary • risk factor analysis

Hypercholesterolemia, diabetes mellitus, hypertension, smoking, and heredity are all associated with an increased risk of coronary heart disease.1–5 However, there have been few clinical studies on the etiology of vasospastic angina,6 and the role of the various risk factors has usually been assessed on the basis of a clinical diagnosis rather than a pathological or angiographic examination. The objective of this study was to examine the risk factors for coronary vasospasm through a retrospective comparison of patients with angiographically determined vasospastic angina with subjects with angiographically normal coronary arteries.

Methods

Patients

From patients who underwent diagnostic coronary arteriography between March 1975 and December 1990, we selected 351 subjects who fulfilled study criteria. Group 1 (vasospasm group) consisted of 175 patients (165 men and 10 women) with no coronary artery luminal narrowing >25% but who showed (either spontaneously or after administration of ergonovine maleate) spasm in one or more of the epicardial coronary arteries during coronary arteriography. All 175 patients had chest pain; most of them had rest or nocturnal pain, with or without pain on exercise, but a few of them had only exertional chest pain. Coronary spasm was defined as ≥75% luminal narrowing (129 patients showed >99% spasm). Their ages ranged from 33 to 76 years (mean, 55 years). Of these 175 patients, 99 had spasm in one coronary artery, 67 patients had spasm in two vessels, 20 patients had spasm in all three major vessels, and one patient had spasm in the left main trunk as well as in the left anterior descending artery. Group 2 (control group) consisted of 176 subjects (110 men and 66 women) with completely normal coronary arteries and without spasms that reduced the luminal diameter by >50% (either spontaneous or after ergonovine maleate). In this group, coronary arteriography was performed to investigate atypical chest pain not relieved by sublingual nitrates, ECG abnormalities at rest or after exercise, or hyperlipemia associated with one of those two features. The age range of this group was 34 to 81 years (mean, 56 years). Among the other 8,740 patients excluded from the study, 5,260 patients were excluded because of the presence of significant (≥75% decrease in diameter) narrowing in at least one coronary artery or a definite history of myocardial infarction (prolonged chest pain, serial ECG changes, and elevation of cardiac enzymes). Another 2,822 patients were excluded because ergonovine provocation was not performed for the following reasons: 1) the possible risk of side effects in patients with remarkable hypertension or renal failure, 2) a diagnosis of valvular heart disease or cardiomyopathy without chest pain, 3) coronary arteriography was performed before ergonovine maleate came into clinical use (156 patients) or provocation testing was refused (20 patients). Another 640 subjects in whom the clinical or angiographic diagnosis was equivocal or indeterminate were excluded for the following reasons: 1) moderate coronary atherosclerosis (25–75% decrease in luminal diameter), 2) no response to provoca-
tion despite symptoms suggesting variant angina (resting or nocturnal chest pain relieved by sublingual nitrates), since a lack of response to ergonovine was not considered to rule out the possibility of spontaneous vasospasm, 3) equivocal angiographic findings (transient coronary narrows encroaching the lumen by ≥50% but <75% either spontaneously or after ergonovine).

Patients who had previously quit smoking before the onset of chest pain (in group 1) or before suspicion of coronary artery disease (in group 2) were also excluded to simplify the analysis of risk factors and because the number was too small to analyze independently; there would have been 15 such patients in group 1 and three in group 2.

**Coronary arteriography.** Arteriography was performed after the withdrawal of calcium antagonists, β-blockers, and long-acting nitrates for at least 48 hours. Pentazosine (15 mg) was administered intramuscularly 30 minutes before the study. A Sones catheter was inserted by brachial arteriotomy. The right coronary artery was visualized in the left anterior oblique view and the left coronary artery in the right anterior oblique view. The catheter was placed in the left coronary ostium, and 0.2 mg of ergonovine maleate was injected intravenously. If the initial arteriogram suggested considerable spasm, only 0.1 mg of ergonovine maleate was given, and this was followed by an additional 0.2 mg of ergonovine if no spasm occurred. If the patient felt chest discomfort or if ST segment changes were seen on the standard 12-lead ECG, the left coronary artery was filled with contrast immediately, and the right coronary artery was imaged within 1 minute after left coronary arteriography. If no chest discomfort or ECG changes appeared, the left and right coronary arteriograms were performed 2 minutes after ergonovine maleate administration. Sublingual nitroglycerin or intravenous or intracoronary isosorbide dinitrate (5–10 mg) was given, and coronary arteriograms were obtained in multiple projections.

**Risk factors.** A smoking history was obtained from all the patients on admission. All the smokers were cigarette smokers, and if their cigarette consumption varied significantly from day to day, the mean value was defined as one seventh of the weekly consumption. All the smokers had smoked for more than 20 years. Blood pressure was measured at least three times when the subject was unmedicated, and the mean of the measured values was used. Total cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides were measured on the morning of angiography with the subjects fasting.

Hypercholesterolemia was defined as a cholesterol level >250 mg/dl, a reduced HDL-cholesterol level was defined as <40 mg/dl, a raised low density lipoprotein (LDL) cholesterol level as >160 mg/dl, and a high triglyceride level was defined as >170 mg/dl. A glucose tolerance test was also performed on the morning of the angiographic study and was interpreted according to the World Health Organization criteria. Total cholesterol, HDL-cholesterol, and triglyceride levels were measured in 351 subjects from the two groups. The triglyceride level was <300 mg/dl in 331 subjects, and for them the LDL-cholesterol level was calculated using the following equation: LDL-cholesterol = (total cholesterol − HDL-cholesterol) × ⅔ triglycerides. The body mass index (BMI) was calculated as weight (kg)/height (m)² and obesity was defined as a BMI >26. Hypertension was defined as a systolic blood pressure of ≥160 mm Hg. Because smoking is still far more common in men than in women in Japan, the same risk factor analyses were performed for the men in each subgroup. This was not done for women because of the small number of female patients in group 1.

**Statistical Analysis**

All the risk factors were first assessed individually using odds ratios. Statistical significance was defined by 95% confidence intervals not crossing unity. Subsequently, all the factors were considered in a multivariate model using logistic regression.

On the multivariate logistic regression, analysis was performed using the SAS software package 8.10 for all the risk factors (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, BMI, hypertension, diabetes mellitus, smoking), age, and sex. Hypertension, diabetes mellitus, smoking, and sex were included as categorical variables. Total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, BMI, and age were included as continuous variables.

**Results**

The prevalence of risk factors is shown in Table 1. Among the 175 patients with vasospastic angina, 159 (91%) were smokers, whereas only 51% (90 of 176) of the normal control subjects were smokers. The mean age was 55 years for patients with vasospastic angina and 56 years for normal control subjects. The mean age and sex-adjusted values (and SEM) for the risk factors obtained by regression analysis are shown in Table 2. There were no differences between the two groups regarding total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, and the total cholesterol/HDL-cholesterol ratio. Smoking was markedly more prominent in the vasospasm group even after adjustment for age and sex.

Crude and adjusted odds ratio estimates and 95% confidence intervals for each of the variables are presented in Tables 3 and 4. The crude odds ratio of smokers compared with normal control subjects was 4.3 for vasospasm (95% confidence interval, 2.70–7.01)
The adjusted odds ratio of smokers for vasospasm was 2.41 (95% confidence interval, 1.53–3.82), indicating a significant association between smoking and vasospasm. As demonstrated by the crude and adjusted odds ratios and confidence intervals presented in Tables 3 and 4, no positive relation was observed between vasospasm and elevated levels of high total cholesterol, LDL-cholesterol, or high triglyceride levels, low HDL-cholesterol, presence of diabetes mellitus, or BMI. Paradoxically, hypertensive subjects showed a lower risk for vasospastic angina, with an adjusted odds ratio of 0.57 for subjects with hypertension (95% confidence interval, 0.40–0.81).

The same analyses performed in men only, as described in “Methods,” showed similar results. The adjusted odds ratio of male smokers for vasospasm was 2.30 (95% confidence interval, 1.39–3.81), showing significant association between vasospasm and smoking.

The adjusted odds ratios and 95% confidence intervals were similar in analyses in men only: elevated levels of high total cholesterol, odds ratio 0.85, (95% confidence interval, 0.34–2.09); elevated levels of LDL-cholesterol, 0.67, (0.27–1.69); high triglyceride levels, 1.02 (0.83–1.27); low HDL-cholesterol levels, 1.01 (0.69–1.50); presence of diabetes mellitus, 0.68 (0.41–1.14); and BMI, 0.95 (0.51–1.74). Also in men only, hypertensive subjects showed a lower risk for vasospastic angina, with an adjusted odds ratio of 0.65 for subjects with hypertension (95% confidence interval, 0.45–0.94).

**Discussion**

The purpose of the present study was to assess the risk factors for vasospastic angina, as was previously attempted by Scholl et al. The method of subject selection we used was quite different from that of Scholl et al, who defined groups on the basis of history alone (control group, group 2) or ECG and angiography (vasospasm group, group 1). We consider that these criteria are not sufficiently strict because moderate coronary atherosclerosis can be present in the absence of chest pain and ST segment elevation is not always observed in patients with coronary spasm. Accordingly, we tried to select only subjects with “pure” vasospasm and completely normal coronary arteries by using strict arteriographic criteria as well as the clinical findings. Despite these differences in selection criteria, our results were very similar to theirs regarding the relation between smoking and coronary vasospasm and the lack of a role for hyperlipidemia, diabetes mellitus, hypertension, and obesity in the pathogenesis of vasospastic angina.

These findings suggest that the pathogenesis of coronary vasospasm unassociated with significant coronary atherosclerosis differs from that of atherosclerosis because hyperlipidemia, diabetes mellitus, obesity, and hypertension have already been shown to be significant factors contributing to coronary artery disease. Smoking has been recognized as one of the major risk factors for myocardial infarction, sudden death, and angina pectoris, so it seems possible that it may contribute to coronary ischemia at least partly by producing vasospasm. After investigating risk factors in 10 patients with recent myocardial infarction whose coronary arteries showed no significant angiographic narrowing, McKenna et al reported recently that smoking was the sole significant risk factor. They also described the postmortem findings of two patients who died of acute myocardial infarction in whom they found occlusive coronary thrombosis without atheromatous changes. Thus, even in individuals with myocardial infarction, coronary atherosclerosis is not always present. Therefore, when investigating the etiology of coronary artery disease, pathological or angiographic data on the

**Table 2. Values Obtained by Regression Analysis of Risk Factors, Adjusted for Age and Sex**

<table>
<thead>
<tr>
<th>Patients with vasospasm</th>
<th>Smoking (cigarettes/day)</th>
<th>Total chol (mg/dl)</th>
<th>TG (mg/dl)</th>
<th>HDL-cholesterol (mg/dl)</th>
<th>Total/HDL-cholesterol ratio</th>
<th>LDL-cholesterol (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>175</td>
<td>19.5±1.6*</td>
<td>204±3.8†</td>
<td>154±7.7†</td>
<td>53±1.6†</td>
<td>4.3±0.18†</td>
</tr>
<tr>
<td>Control subjects</td>
<td>176</td>
<td>11.6±1.3*</td>
<td>209±3.1†</td>
<td>148±6.4†</td>
<td>54±1.3†</td>
<td>4.2±0.15†</td>
</tr>
</tbody>
</table>

All values are mean±SEM. Chol, cholesterol; TG, triglycerides; HDL, high density lipoprotein; LDL, low density lipoprotein.

*p<0.001, †p=NS.

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**Table 3. Comparison of Risk Factors Between Patients With Vasospasm and Normal Control Subjects, Crude Odds Ratios**

<table>
<thead>
<tr>
<th>Crude odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>4.35</td>
</tr>
<tr>
<td>Total cholesterol &gt;250 mg/dl</td>
<td>0.66</td>
</tr>
<tr>
<td>LDL-cholesterol &gt;160 mg/dl</td>
<td>0.89</td>
</tr>
<tr>
<td>HDL-cholesterol &lt;40 mg/dl</td>
<td>0.80</td>
</tr>
<tr>
<td>TG &gt;170 mg/dl</td>
<td>1.06</td>
</tr>
<tr>
<td>BMI &gt;26</td>
<td>0.77</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.84</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.14</td>
</tr>
</tbody>
</table>

LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglycerides; BMI, body mass index.

**Table 4. Adjusted Odds Ratios Derived From Logistic Regression Analysis for Patients With Vasospasm Versus Normal Control Subjects, Adjusted for Age, Sex, and All Risk Factors**

<table>
<thead>
<tr>
<th>Adjusted odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>2.41</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.75</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>0.77</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.07</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.03</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.84</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>0.57</td>
</tr>
</tbody>
</table>

LDL, low density lipoprotein; HDL, high density lipoprotein.
nary arteries are necessary because of the possibility that coronary artery spasm and not atherosclerosis is the cause of ischemia even when angina pectoris or myocardial infarction is diagnosed clinically. Of course, our results do not suggest that smoking is not one of the major causes of coronary atherosclerosis. In addition, it is possible that our vasospastic angina patients without any apparent coronary narrowing actually had very mild atherosclerosis that was not visible on their arteriograms and that this played some role in the development of vasospasm.

It is difficult to explain why a low blood pressure rather than high blood pressure was positively associated with vasospasm. It is possible that the presence of hypertension or an ECG abnormality produced by hypertension was the reason for the performance of coronary arteriography in some subjects in the control group. However, this apparently paradoxical finding also suggests that the pathogenesis of vasospasm differs from that of coronary atherosclerosis.

Conclusions

Smoking appears to be the major risk factor associated with coronary vasospasm in patients without significant angiographic coronary stenosis.

References

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