CORONARY ARTERIAL SPASM was long considered the main mechanism in angina pectoris until the recognition of fixed atherosclerotic narrowing in association with angina led to a revision of that concept. In the last few years, the role of spasm is again being discussed because of the coronary angiographic demonstration of the phenomenon.

Coronary artery spasm is an important, if not the most important, feature of variant angina. It is possible that coronary arterial spasm could play a significant role throughout the wide spectrum of ischemic heart disease. The incidence of spasm in the patient undergoing coronary arteriography is not, however, well documented. In this study we aimed to establish the incidence of spasm provoked pharmacologically in 1089 patients who underwent angiography.

Methods

In May 1979, we started systematically performing provocation tests in all patients who underwent coronary angiography. Subjects were excluded and the provocative test was not performed if there was left main narrowing (even small irregularities), very severe three-vessel disease (e.g., total occlusion of two vessels and severe narrowing of the third), heart failure (New York Heart Association functional class III or IV), or if spontaneous spasm was observed. Two hundred forty-one patients were excluded. From June 1, 1979, to October 31, 1980, provocation tests using methergine were performed in 1089 consecutive patients undergoing coronary angiography.

The procedure was explained to each patient and it was indicated that detection of coronary arterial spasm could lead to the use of special drugs, i.e., calcium antagonists. All patients gave informed consent.

Patients were categorized by their symptoms. Typical angina was defined as retrosternal pain that radiated down the inner aspect of the left arm, to the lower jaw, neck or teeth and was described as strangled, constricting or crushing and was quickly (less than 5 minutes) relieved by nitroglycerin. Angina of effort was characterized by transient episodes of angina precipitated by exercise; angina at rest, by episodes of pain occurring without apparent relation to increased myocardial oxygen demand. When these criteria were not met, the symptoms were classified as atypical chest pain.

Clinically, the patients fell into six groups. Group A included 248 patients (mean age 49.4 ± 7.2 years) with atypical chest pain. They did not have the characteristics of typical chest pain and presented only one or two features suggestive of angina.

Group B included 255 patients with typical angina of effort. Two hundred eleven had exercise tests, of whom 178 had positive tests. Group B was further subdivided into subgroup B1, which included 117 patients (mean age 51.4 ± 6.5 years) with exertional angina alone, and subgroup B2, which included 138 patients (mean age 54.5 ± 6.5 years) in whom angina was mainly precipitated by exercise, but occasionally occurred at rest. Long-term ambulatory Holter
monitoring was performed during admission. Transient ST-segment changes were observed in only 14 of these: ST elevation in eight, ST depression in five and T-wave changes in one.

Group C included 203 patients (mean age 51.2 ± 8.5 years) who suffered one or more episodes of angina that were always unrelated to exercise and most often nocturnal. During admission, 24-hour Holter monitoring was performed and complete 12-lead ECGs were recorded when the patient had an attack of angina. Some did not suffer further attacks during admission. During attacks, transient ST-segment changes were demonstrated in 78 patients: ST elevation in 59, ST depression in 11 and T-wave changes in eight. In the 125 remaining patients who were pain-free throughout admission, no changes were observed by continuous Holter monitoring.

Group D included 180 patients who had suffered myocardial infarction. All were asymptomatic, but in our institution, coronary angiography was systematically performed after myocardial infarction to document the state of the coronary arteries and to establish the prognosis.

Group D was subdivided: subgroup D1 included 116 patients (mean age 49.6 ± 0.9 years) in whom coronary angiography was performed within 6 weeks of the onset of the infarction, and subgroup D2 included 65 patients (mean age 51.1 ± 8.5 years) who were investigated later.

Group E included 154 patients with valvular disease. Some had pain; all were at least 40 years old and underwent catheterization to evaluate valvular disease; coronary arteriography is routine in such patients over age 40 years. Seventy-one patients had mitral valve disease (stenois, regurgitation or both); six of them had mitral valve prolapse. Fifty had aortic valve disease (stenosis, regurgitation or both) and 33 had mitral disease with associated aortic disease.

Group F included 49 patients with congestive cardiomyopathy. The protocol included right- and left-heart catheterization, left ventriculography and coronary arteriography. These patients also underwent provocative testing.

Provocation Test

Provocation was performed after routine coronary angiography. Left ventricular and aortic pressures were measured and cardiac output was estimated in duplicate by dye dilution. Left ventriculography was carried out in the 30° right anterior oblique projection and in the lateral position. Cineangiography was performed at 50 frames/sec. The Judkins technique was used with a Bourassa catheter and an introducer sheath incorporating hemostatic valves (Cordis 501-608).20 The left coronary artery was examined in five radiologic projections, including two with a cranial tilt. The right coronary artery was examined in four projections, including two with a sagittal tilt. Before the provocation test, a preliminary angiogram as a control was performed in the lateral projection (intensifier image on the left side of the patient). An ECG was recorded from leads I, III and V2.

A simultaneous recording was made of the aortic pressure. Methylergonovine maleate (Methergine), 0.4 mg, was given as a bolus into the femoral vein.21 The coronary artery was opacified 3–5 minutes later. After opacification of the vessel (usually the right coronary artery), at the fifth minute, the catheter for the left coronary artery was introduced to visualize this vessel. The rapid changeover was facilitated with use of a sheath.20 If, before the third minute chest pain and electrocardiographic changes supervened (elevation or depression of the ST segment), the vessel corresponding to the electrocardiographic abnormality was immediately infused with dye. If the criteria of spasm were fulfilled, an immediate dose of isosorbide dinitrate (3–5 mg) was administered either intravenously or directly into the affected vessel. The opacification was then repeated every minute to monitor the disappearance of the localized spasm. During the entire procedure, the ECG and aortic pressure were closely monitored.

In the patients with a typical history of angina, normal coronary arteriograms and without provoked spasm, a #8F Gorlin pacing catheter was advanced to the midportion of the coronary sinus. The pacing rate was increased by 10 beats/min until the onset of angina, the occurrence of noncapture or a rate of 160 beats/min was achieved. Blood samples for lactate were obtained from the coronary sinus and aorta when heart rate reached 120, 140 or 160 beats/min.

Angiographic Analysis

The coronary arteriograms were analyzed separately by two independent observers. Coronary artery spasm was assessed according to the criteria described by Chahine et al.22: (1) appearance of total occlusion of a segment of normal coronary artery or at the site of atherosclerotic narrowing (fig. 1); (2) appearance of significant narrowing (more than 75%) of a segment of coronary artery that was initially or subsequently considered to be normal (fig. 2); (3) the disappearance, either spontaneous or induced by pharmacologic agents (in particular nitroglycerin and its derivatives), of the narrowing or occlusion.

The catheter-induced spasm (localized to the segment of artery adjacent to the catheter tip) and the diffuse insignificant narrowing seen throughout any vessel, were excluded from this study. Thus, focal spasm fulfilling the above criteria was the only spasm considered.

If a lesion varied in severity from one view to another, it was graded according to its worse appearance in any one view. The severity of the vessel disease was classified as: 0 = lumen perfectly smooth and even; 1 = irregularities; 2 = reduction of luminal diameter by 25–50%; 3 = luminal reduction of 50–75%; 4 = luminal reduction of 75–99%; and 5 = total occlusion. Lesions with 50% luminal reduction or more were considered to be significant.

Statistical Methods

Contingency table analysis using chi-square tests of significance was used to compare the incidence of spasm.
Results

The results are summarized in table 1.

Group A

Of the 248 patients with atypical chest pain, 221 (89%) had normal or near-normal vessels (grade I). Twenty-two (9%) had one-, five (2%) two- and none three-vessel disease. Methylene provoked spasm in three patients (1.2%), all women. All had insignificant vessel disease by angiography. Spasm was located in the midportion of the right coronary artery in two cases and in the left circumflex artery in one. Only one of the three had chest pain and ST-segment elevation; the two others had neither pain nor ECG changes.

Group B

In subgroup B1 (patients who experienced exertional angina of effort without any rest pain), 38 (32.5%) had one-, 26 (22.2%) two- and 30 (25.6%) three-vessel disease; 23 had insignificant disease. Only five patients had focal spasm. Four had pain and three ECG changes during spasm. Thus, the frequency of focal spasm was very low (4.3%) in the context of angina of effort. Three of these five had insignificant vessel disease. One had one- and one had three-vessel disease. Coronary spasm was in the right coronary artery in four cases (midportion in three and distally, proximal to the crux in one). One patient had spasm that totally occluded the first diagonal artery. In the 23 patients with exertional angina and angiographically normal coronary arteries, only three had spasm; 13 had no spasm, but had myocardial lactate production during the tachycardia induced by atrial pacing.

In subgroup B2 (patients who experienced exertional angina with some episodes of angina at rest), 14 patients had ST-segment changes during attacks at rest. Twenty-two patients (16%) had one-, 34 (24.6%) two- and 24 (17.4%) three-vessel disease; 58 (42%) had insignificant disease. Spasm was more frequent in this subgroup than in subgroup B1 (p < 0.01). Nineteen patients (13.8%) had angiographic evidence of coronary arterial spasm. During spasm, 89% of patients had chest pain and 56% had ECG changes. Eight of the 14 patients with documented ST-segment changes during angina at rest had coronary arterial spasm. Among the 58 patients of this subgroup with normal vessels or insignificant stenosis, only four had spasm; in the other patients a coronary sinus sampling catheter with pacing electrodes was positioned in the midportion of the coronary sinus. The heart rate was increased by coronary sinus pacing and simultaneous arterial and coronary sinus blood samples for determination of lactate were obtained. Thirty patients had myocardial lactate production, indicating anaerobic metabolism. This association of angina with normal or near-normal angiograms and myocardial lactate production (syndrome X) was very frequent in this group.

When episodes of angina at rest were associated with angina of effort (subgroup B2), the frequency of coronary arterial spasm was significantly (p < 0.01) greater than in subgroup B1 (table 2).

Group C

Among the 203 patients with angina at rest, 110 (54%) had significant coronary artery lesions. Fifty-five patients (27%) had one-, 29 (14.2%) two- and 26 (13%) three-vessel disease; 93 patients (45.8%) had only insignificant lesions. The provocation test was
most successful in inducing coronary arterial spasm in this group (77 patients, 38%). This rate was significantly ($p < 0.01$) greater than that in groups A, B1 or B2 (table 2). During spasm, 74% of patients had angina and 78% had ECG changes. However, in our protocol, if spasm occurred, it was treated before the appearance of pain or ECG changes.

Among the 59 patients in whom ST-segment elevation was recorded during angina at rest before coronary arteriography, provocative testing induced spasm in 50 (85%). Among patients with ST-segment depression (11 cases) or T-wave changes (eight cases) recorded during pain at rest, provoked spasm was observed in five patients in each group (45.4% and 62.5%, respectively). Thus, the frequency of provoked spasm was significantly ($p < 0.01$) higher in the group with ST-segment elevation than in the group with ST-segment depression or T-wave changes.

In the 125 patients in whom we could not record the ECG during angina at rest, 64 (51%) had normal or near-normal coronary angiograms. Nineteen patients (15%) had syndrome X and eight (12.5%) had coronary arterial spasm. Sixty-one (49%) had significant coronary lesions: 30 (49%) had one-, 16 (26%) two- and 15 (25%) three-vessel disease. Provoked coronary arterial spasm was documented in nine of these patients. Finally, 134 of the 203 group C patients had chest pain resulting from either significant coronary artery disease or spasm.

**Group D**

The 180 patients with transmural myocardial infarction were subdivided. Subgroup D1 patients had a typical clinical history, development of new Q or QS waves and unequivocal serum enzyme changes, but were asymptomatic. The coronary angiogram and provocation test were performed within 6 weeks of these symptoms. Seventy-one patients (61%) had an anterior infarct, 43 (37%) an inferior infarct and two (2%) a lateral infarct. Fifty-four (46%) had one-, 31 (27%) two- and 24 three-vessel disease; seven (6%) had minimal vessel disease. In 23 (20%), Methergine provoked focal spasm. The spasm was located in the vessel responsible for the infarction in 14 cases (12%). Spasm was located in a vessel unrelated to the area of the infarct in nine cases (8%). None of the seven patients with insignificant disease developed focal spasm; however, in four patients, Methergine induced very

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**Figure 2.** Spasm on the midportion of a right coronary artery with an insignificant lesion. (A) Before the provocation test. (B) Three minutes after methergine. (C) One minute after isosorbide dinitrate.

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**Table 1. Vessel Disease and Frequency of Coronary Artery Spasm**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Nonsignif.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Spasm</th>
<th>Comparisons of other groups to group A</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>248</td>
<td>221</td>
<td>22</td>
<td>5</td>
<td>3</td>
<td>1.2%</td>
<td>NS</td>
</tr>
<tr>
<td>B1</td>
<td>117</td>
<td>23</td>
<td>38</td>
<td>26</td>
<td>30</td>
<td>4.3%</td>
<td>NS</td>
</tr>
<tr>
<td>B2</td>
<td>138</td>
<td>58</td>
<td>22</td>
<td>34</td>
<td>24</td>
<td>13.8%</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>C</td>
<td>203</td>
<td>93</td>
<td>55</td>
<td>29</td>
<td>26</td>
<td>48%</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>D1</td>
<td>116</td>
<td>7</td>
<td>54</td>
<td>31</td>
<td>24</td>
<td>20%</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>D2</td>
<td>64</td>
<td>3</td>
<td>26</td>
<td>20</td>
<td>15</td>
<td>6.2%</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
<td>E</td>
<td>154</td>
<td>132</td>
<td>16</td>
<td>5</td>
<td>1</td>
<td>2%</td>
<td>NS</td>
</tr>
<tr>
<td>F</td>
<td>49</td>
<td>44</td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>1089</td>
<td>581</td>
<td>237</td>
<td>151</td>
<td>120</td>
<td>134</td>
<td></td>
</tr>
</tbody>
</table>

See text for definitions of groups.
severe diffuse narrowing in the vessel responsible for the infarction.

The incidence of focal spasm was significantly higher \((p < 0.001)\) soon after myocardial infarction than in exertional angina or atypical chest pain but was lower \((p < 0.001)\) than in patients with angina at rest. However, the frequency of provoked spasm was different (NS) in patients with recent myocardial infarction and those who experienced chest pain during exercise and at rest. During the spasm, 78% of patients had no ECG changes but 43% experienced chest pain.

The 64 patients in subgroup D2 were investigated after a longer interval. Twenty-six (41%) had one-, 20 (31%) two- and 15 (23%) three-vessel disease; only three patients (5%) had insignificant disease. Only four patients (6.2%) had coronary arterial spasm, and it was, in all cases, located in vessels unrelated to the area of infarct. The incidence of spasm was significantly \((p < 0.05)\) lower in subgroup D2 than in subgroup D1.

Group E

Of the 154 patients in group E, 132 (85.7%) had normal coronary arteriograms; 16 (10%) had one-, five had two- and one three-vessel disease. Methylene in-

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Table 2. Differences Between the Various Groups of Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>A</th>
<th>B1</th>
<th>B2</th>
<th>C</th>
<th>D1</th>
<th>D2</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spasm</td>
<td>3</td>
<td>5</td>
<td>19</td>
<td>77</td>
<td>23</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>No spasm</td>
<td>245</td>
<td>112</td>
<td>119</td>
<td>126</td>
<td>93</td>
<td>60</td>
<td>151</td>
<td>49</td>
</tr>
</tbody>
</table>

See text for definitions of groups.

\* \(p < 0.05\).

\(\dagger p < 0.01\).

\(\ddagger p < 0.001\).

Overall Results

Figure 3 is a summary of the results from the study of all 1089 patients. The provocation test caused coronary arterial spasm in 134 patients (12.3%). Considering only the 886 patients with chest pain or a history of myocardial infarction, the frequency of spasm was 15%. Ninety-six of 134 cases with spasm occurred among patients who complained of angina at rest, whether associated with angina of effort or not. In cases in which angina at rest was associated with angina of effort, spasm was less frequent (13.8%) than when angina occurred only at rest (38%). In 67 patients, the diagnosis of variant angina was made before coronary angiography and on the basis of pain at rest with associated ST-segment elevation. In this group, the provocation test achieved a particularly high incidence of spasm (85.1%). The frequency of
spasm in asymptomatic patients with recent transmural infarction was 20%, compared with 5.2% among patients investigated later.

Characteristics of the Observed Spasm

In 79 cases (59%), spasm was superimposed on fixed organic atherosclerotic narrowings; 55 (41%) in whom provoked spasm was observed had insignificant lesions or normal coronary angiograms. The spasm occurred most often in the right coronary artery (68 cases [51%]) and the left anterior descending coronary artery (41 cases [30%]). The circumflex artery was the site of spasm in only 15 cases (11%). Three patients (2.2%) had spasm in the right and left anterior descending arteries simultaneously. Three others suffered spasm in both LAD and circumflex arteries and two patients had spasm in both LAD and diagonal arteries. One patient had spasm in the circumflex and RCA, while one had spasm in all three vessels.

Complications

No serious irreversible complications occurred. Four patients developed ventricular fibrillation, which was immediately reversed by cardioversion. One patient developed a short run of ventricular tachycardia that resolved immediately with the treatment of the spasm. Another patient had third-degree atrioventricular block with a heart rate of 40 beats/min, reversed by atropine. Another developed a sinus bradycardia, easily reversed by 0.75 mg of atropine. Thus, seven complications (0.64%) were noted, none irreversible or with serious consequences. However, all of the complications were in patients with coronary artery spasm; in this subgroup, the incidence was 5.2%.

Increasingly large doses of Methylene blue have been used,23-25 sometimes reaching doses higher than the dose we used in a single bolus. In our experience, a single bolus of 0.4 mg does not carry a substantial risk. Although the complications were minor and reversible, they were noteworthy. Some insist that the provocation test should be carried out in the intensive care unit. We strongly advise that the test be performed in a room with angiographic facilities where it is possible to recognize severe atherosclerotic lesions such as extreme narrowing of the left main coronary artery, and thus avoid performing the test in these cases.26 Angiography is the only means of obtaining direct proof of spasm and it is essential to terminate the spasm as quickly as possible once it has been documented. When the test is performed without angiographic facilities, reversal of spasm by nitrates is only done when ECG changes have been observed, and this is always later than anatomic change in the coronary vessel. Moreover, when the test is performed during coronary angiography, relief of spasm is easily achieved by direct injection of nitroglycerin into the affected vessel. The absence of refractory spasm26 and the low incidence of complications are evidence that our procedure is safe.

Discussion

Coronary arterial spasm was proposed as a mechanism for angina more than a century ago. It was neglected in the light of pathologic studies and, more recently, coronary angiographic demonstration of fixed atherosclerotic lesions. It has become increasingly apparent that myocardial ischemia was not necessarily preceded by increased oxygen demand.28, 29 In certain clinical circumstances, a decreased oxygen supply has been shown to result from a reduction in coronary blood flow. A revival of interest in spasm has occurred during the last 4 years, and coronary artery spasm has been suggested as the major factor in the pathophysiology of variant angina. The incidence of spasm in other manifestations of coronary insufficiency is, however, less well documented. The purpose of our study was to establish the frequency of spasm in a population of patients undergoing coronary angiography.

The first important question was whether spasm provoked by Methylene blue was similar to that occurring spontaneously. Our previous studies and those of Curry et al.30 have confirmed the similarities of ergonovine-induced and spontaneous spasm. The second important question concerns the specificity of the phenomenon. We systematically performed the test on patients with various cardiac diseases, including valvular disease and cardiomyopathy. The incidence of provoked spasm was significantly ($p < 0.001$) lower in patients with valvular disease or cardiomyopathy than in the others. Among 203 patients, 175 of whom had normal coronary angiograms, only three (1.5%) developed focal coronary spasm; one of them had angina at rest with ST-segment depression. In the population of patients who experienced coronary events, the overall incidence of spasm was 15.4%. This only represents the incidence in a population of patients undergoing coronary angiography, i.e., patients with severe clinical manifestations, and thus does not represent the true incidence. A large number of our patients had severe pain at rest, because patients with severe pain at rest are admitted to hospital, whereas those with exertional angina are treated on an outpatient basis and only admitted to hospital when pain is refractory to medical treatment. Moreover, 248 patients had atypical chest pain and 221 had normal coronary arteries. If we consider the 665 patients with evidence of coronary disease, 131 (20%) had provoked spasm. This percentage can only be considered as a guide to the frequency of the phenomenon, the problems of the selection of the study population being considered.

During this study, the incidence of spasm was only 4.3% in patients with angina of effort. Some authors31-33 have reported coronary arterial spasm during episodes of angina of effort. Some of the reported patients had ST-segment depression and others had variant angina with exercise-induced chest pain and ST-segment elevation. How spasm is involved in response to exercise is uncertain. We found that most patients in whom spasm was induced had suffered attacks of angina at rest. For example, the incidence of
spasm was significantly ($p < 0.01$) higher when angina at rest was associated with angina of effort (13.7%) than when angina was only induced by effort (4.3%). However, among patients who had angina at rest, only 38% had coronary arterial spasm. Spasm was more common (85%) in patients in whom rest angina was associated with ST-segment elevation.

Our data can provide answers to the pathophysiologic problems of patients with ST-segment depression during angina at rest. Some authors have observed alternating ST-segment elevation and ST-segment depression in patients with angina at rest. However, the extrapolation of results in these patients to patients with ST-segment depression alone is unclear. In our study, 45% of these patients had coronary arterial spasm.

The most difficult problem concerns patients admitted in the coronary care unit with angina at rest, but in whom ECG changes were not recorded during episodes of angina after admission. Forty-nine percent had significant vessel disease, and spasm was superimposed in only 15%. Sixty-four (51%) had normal or near-normal coronary angiograms. Syndrome X was demonstrated in 19%; of the 45 others, spasm was induced in only eight (18%). The mechanism of angina at rest in this group is unclear. Spasm could not be completely excluded because there is great variability of symptoms, even a circadian variability. One can speculate whether a positive provocation test would have been obtained at another time.

The reactivity of vessels just after an infarct was significantly ($p < 0.05$) higher than in the later phase; this supports the previous studies that suggested that spasm could be one of the several causes of acute myocardial infarction. The high degree of reactivity of the vessels suggests that recurrence of pain or even new myocardial infarction could occur in these patients and they could be treated with calcium antagonists.

The last question concerns the indications for performing the provocative test. The test is of no value in patients who experience angina only during exercise. We have found that of the patients subjected to the test, those who complain of angina at rest were those in whom spasm was most frequently induced. Thus, provocation should be used in these patients and, in particular, in those with normal coronary angiograms or minimal lesions.

Spasm was frequently observed superimposed on organic lesions. Taking into account the incidence of coronary arterial spasm and the relative safety of our procedure, this trial has not only been of pathophysiologic interest, but also has therapeutic implications. Although $\beta$ blockers might aggravate spasm, increasing its frequency, calcium antagonists efficiently relieve spasm; recognition of spasm therefore may be important in the management of patients with angina, especially with those who have pain at rest.

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