Local coronary supersensitivity to diverse vasoconstrictive stimuli in patients with variant angina

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ABSTRACT  It has been shown in different groups of patients with variant angina that coronary spasm can be reproduced by physiologic maneuvers and pharmacologic agents. It is not known, however, to what extent different stimuli can induce spasm in the same patient. To investigate whether coronary arterial spasm results from specific abnormal agonist-receptor interactions or from a local nonspecific coronary supersensitivity to different stimuli, 28 patients with vaso spas tic angina were submitted to a series of diverse vasoconstrictive stimuli known to provoke coronary spasm. Ergonovine, hyperventilation, handgrip, cold pressor, and exercise-tests, were carried out in all 28 patients. In the last 15 patients histamine was also administered. Spasm was provoked by ergonovine in 96% of patients, by hyperventilation in 54%, by histamine in 47%, by exercise in 46%, and by the cold pressor and handgrip tests in 11% and 7%, respectively. No significant differences were found in the responses to provocative tests of patients with normal coronary arteries or nonsignificant stenoses and those with significant lesions. In the same individual, spasm was induced by at least two vasoconstrictive stimuli, although with a different mechanism of action, in 82% of patients and spasm was induced by three or more stimuli in 39%. Tests were repeated in at least 23 patients and short-term reproducibility paralleled sensitivity. These results suggest that in patients with variant angina, a local nonspecific supersensitivity rather than an abnormal specific agonist-receptor interaction plays a major role in the genesis of coronary arterial spasm.

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ALTHOUGH coronary arterial spasm is now a well-recognized clinical entity, its causes remain elusive. Based on the observation that in the individual patient with variant angina coronary spasm tends to recur in the same vascular segment, we suggested a decade ago that a local supersensitivity of the coronary vessels to diverse vasoconstrictor stimuli\(^1\) was the mechanism underlying coronary spasm. Specific agonist-receptor interactions have also been proposed as an alternative cause of spasm.\(^2\)–\(^11\) However, attempts to prevent spontaneous or ergonovine-induced coronary spasm with specific blockers failed or produced inconclusive results.\(^12\)–\(^18\)

In patients with variant angina focal coronary spasm can be reproduced by ergonovine\(^19\)–\(^22\) and, less frequently, also by hyperventilation.\(^23\)–\(^25\) Isolated reports suggest that coronary spasm can also be provoked by a number of physiologic maneuvers\(^26\)–\(^29\) and pharmacologic agents such as histamine,\(^9\) epinephrine,\(^3\) meta- choline,\(^5\) and dopamine.\(^30\) It has therefore become apparent in patients with variant angina that particular segments of their epicardial coronary arteries exhibit an abnormal reactivity to stimuli that produce only minor degrees of coronary constriction, if any, in normal individuals or in patients with other forms of angina.\(^31\)

The aim of our study was to investigate whether the abnormal coronary reactivity exhibited by patients with vaso spas tic angina results from specific abnormal agonist-receptor interactions or from a local, nonspecific supersensitivity to different stimuli. To this end, we studied the responses of patients with vaso spas tic angina to a series of provocative tests known to induce coronary spasm through different mechanisms.
TABLE 1  
Clinical, electrocardiographic, and angiographic findings

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)/sex</th>
<th>Onset (months)</th>
<th>Type</th>
<th>No. episodes/wk (2 wk before admission)</th>
<th>Location of previous MI (months since event)</th>
<th>ECG results During angina</th>
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<tbody>
<tr>
<td>1</td>
<td>48/M</td>
<td>3</td>
<td>E+R</td>
<td>30</td>
<td>—</td>
<td>Normal ST ↑ V_{2,5}</td>
</tr>
<tr>
<td>2</td>
<td>56/F</td>
<td>6</td>
<td>R</td>
<td>10-15</td>
<td>—</td>
<td>Normal ST ↑ II-III-F</td>
</tr>
<tr>
<td>3</td>
<td>50/M</td>
<td>2</td>
<td>R</td>
<td>10</td>
<td>—</td>
<td>Normal ST ↑ V_{2,5}</td>
</tr>
<tr>
<td>4</td>
<td>42/M</td>
<td>7</td>
<td>E+R</td>
<td>15 INF (12)</td>
<td>—</td>
<td>Normal ST ↑ V_{1,4}</td>
</tr>
<tr>
<td>5</td>
<td>40/M</td>
<td>2</td>
<td>E+R</td>
<td>10-12</td>
<td>—</td>
<td>Normal ST ↑ V_{2,4}</td>
</tr>
<tr>
<td>6</td>
<td>56/M</td>
<td>24</td>
<td>E+R</td>
<td>10</td>
<td>—</td>
<td>Normal ST ↑ V_{1,4}</td>
</tr>
<tr>
<td>7</td>
<td>58/M</td>
<td>4</td>
<td>E+R</td>
<td>10 INF (3)</td>
<td>—</td>
<td>Normal ST ↑ V_{1,2}</td>
</tr>
<tr>
<td>8</td>
<td>55/M</td>
<td>2</td>
<td>E+R</td>
<td>14</td>
<td>—</td>
<td>Normal ST ↑ V_{2,3}</td>
</tr>
<tr>
<td>9</td>
<td>66/M</td>
<td>3</td>
<td>R</td>
<td>15</td>
<td>—</td>
<td>Normal ST ↑ V_{1,3}</td>
</tr>
<tr>
<td>10</td>
<td>46/F</td>
<td>6</td>
<td>E+R</td>
<td>12-15</td>
<td>—</td>
<td>Normal ST ↑ V_{2,5}</td>
</tr>
<tr>
<td>11</td>
<td>55/M</td>
<td>6</td>
<td>R</td>
<td>10-14</td>
<td>—</td>
<td>Normal ST ↑ II-III-F</td>
</tr>
<tr>
<td>12</td>
<td>49/F</td>
<td>0.5 (2 wk)</td>
<td>R</td>
<td>10</td>
<td>—</td>
<td>Normal ST ↑ V_{1,3}</td>
</tr>
<tr>
<td>13</td>
<td>46/M</td>
<td>3</td>
<td>R</td>
<td>10-15</td>
<td>INF (3)</td>
<td>qIII-F ST ↑ II-III-F</td>
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<tr>
<td>14</td>
<td>38/M</td>
<td>8</td>
<td>E+R</td>
<td>14</td>
<td>qIII-F</td>
<td>ST ↑ V_{4}</td>
</tr>
<tr>
<td>15</td>
<td>64/F</td>
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<td>14</td>
<td>—</td>
<td>Normal ST ↑ V_{2,5}</td>
</tr>
<tr>
<td>16</td>
<td>53/M</td>
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<td>R</td>
<td>10</td>
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</tr>
<tr>
<td>17</td>
<td>46/M</td>
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</tr>
<tr>
<td>18</td>
<td>50/M</td>
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<td>10-15</td>
<td>AF</td>
<td>ST ↑ I-aVL</td>
</tr>
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<td>3</td>
<td>R</td>
<td>15</td>
<td>—</td>
<td>Normal ST ↑ II-III-F</td>
</tr>
<tr>
<td>20</td>
<td>53/M</td>
<td>2.5</td>
<td>E+R</td>
<td>10-15</td>
<td>—</td>
<td>AF ST ↑ V_{2,6}</td>
</tr>
<tr>
<td>21</td>
<td>67/M</td>
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<td>E+R</td>
<td>10</td>
<td>—</td>
<td>T ↓ V_{1-4} ST ↑ I-3, T ↑ V_{1,2}</td>
</tr>
<tr>
<td>22</td>
<td>54/M</td>
<td>60</td>
<td>R</td>
<td>10-15</td>
<td>—</td>
<td>Normal ST ↑ V_{2,5}</td>
</tr>
<tr>
<td>23</td>
<td>56/M</td>
<td>18</td>
<td>R</td>
<td>12 INF (12)</td>
<td>QII-III-F</td>
<td>ST ↑ V_{4,6}</td>
</tr>
<tr>
<td>24</td>
<td>32/M</td>
<td>0.5 (2 wk)</td>
<td>R</td>
<td>10</td>
<td>—</td>
<td>Normal ST ↑ V_{2,3}</td>
</tr>
<tr>
<td>25</td>
<td>50/F</td>
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<td>R</td>
<td>10</td>
<td>—</td>
<td>Normal ST ↑ V_{1,4}</td>
</tr>
<tr>
<td>26</td>
<td>48/M</td>
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<td>R</td>
<td>14</td>
<td>—</td>
<td>Normal ST ↑ V_{3,4}</td>
</tr>
<tr>
<td>27</td>
<td>35/F</td>
<td>2</td>
<td>R</td>
<td>10 INF (3)</td>
<td>QII-III-F</td>
<td>ST ↑ V_{1,6}</td>
</tr>
<tr>
<td>28</td>
<td>48/F</td>
<td>2</td>
<td>E+R</td>
<td>10-14</td>
<td>—</td>
<td>Normal ST ↑ V_{1,5}</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; Cx = left circumflex; CPT = cold pressor test; Diag = diagonal branch; E = on effort; Ergo = ergonovine; HG = handgrip test; HV = hyperventilation; INF = inferior; irreg = irregularities; LAD = left anterior descending artery; LMS = left main stem; R = at rest; RCA = right coronary artery; RPD = posterodescending branch of the right coronary; Spont = spontaneous; T ↓ = T wave inversion.

Methods

Patients. Of 31 patients with vasospastic angina studied in our institution over the past 5 years (1980–1985), 28 (21 men and seven women, 32 to 67 years old, mean 50) with angiographically documented coronary arterial spasm underwent, within 1 week, all of the following provocative tests: ergonovine, hyperventilation, cold pressor, handgrip, and exercise. The last 15 patients also underwent provocative testing with histamine. All 28 patients had angina at rest, usually nocturnal and in the early morning hours, associated with transient ST segment elevation (26 patients) or depression (two patients). Both anginal attacks and ischemic electrocardiographic (ECG) changes were usually relieved within 3 min by sublingual nitrates. All patients were in an active phase of their disease at the time of admission to the hospital (≥10 episodes of angina per week). Onset of angina ranged from 2 weeks (three patients) to 60 months previously. Eleven of the 28 patients also experienced effort-related angina. No patients had conduction disturbances or left ventricular hypertrophy. Individual clinical, ECG, and angiographic findings are summarized in table 1.

Study protocol. The study protocol was approved by the hospital’s ethics committee and written informed consent was obtained in all cases. Patients were admitted to the coronary care unit and received no antiangiinal therapy, with the exception of sublingual nitrates if required, for at least 48 hr before testing. Investigations were carried out between 10 A.M. and 5 P.M. to minimize bias due to circadian variations in the response to provocative tests. Patients were fasting and had not received nitrates or smoked for at least 2 and 12 hr, respectively. During the first week all patients underwent ergonovine, hyperventilation, histamine, cold pressor, handgrip, and exercise testing. The order in which tests were done was based on availability of personnel and laboratory schedules and the interval between two tests was never shorter than 2 hr. In most patients (detailed below) repeat testing was performed on the basis of availability alone within 2 weeks (1.6 ± 0.8 weeks). Coronary angiographic examinations were performed in all 28 patients and one
or two of the provocative tests known to have produced ischemic ECG changes were repeated during the procedure (table 1). Coronary arteries were considered “normal” if no reductions in luminal diameter were observed; stenoses causing diameter reductions of 50% or less were interpreted as “nonsignificant” and those causing reductions of greater than 50% in at least one major epicardial vessel were considered “significant stenoses.” Three patients (Nos. 6, 15, and 16) underwent repeated provocative testing during recurrence of their symptoms (second “hot phase”) after a quiescent period of 36, 8, and 24 months, respectively.

**Provocative tests.** Apart from the provocative tests carried out during diagnostic angiography, all tests were performed noninvasively in the exercise laboratory adjacent to the catheterization room under continuous computerized ECG monitoring (CASE, Marquette).

Patients were instructed to report immediately the presence of angina or any other symptom during testing. Twelve-lead electrocardiograms were obtained every 30 sec to 1 min throughout the test and for at least 15 min during recovery. Blood pressure was taken before the test and every minute during test and recovery. When ischemic ST segment changes occurred (in most cases accompanied by angina), tests were immediately terminated and isosorbide dinitrate was administered intravenously. When nitrates were required, no other tests were done on that day.

**Ergonovine.** Increasing doses of intravenous ergonovine (25, 50, 100, 200, and up to a maximum of 300 μg) were given at 5 min intervals until angina and ST changes developed.

**Hyperventilation.** Patients were asked to hyperventilate vigorously (>30 cycles/min) over 5 min.

**Cold pressor.** Patients were asked to immerse the right hand and forearm in ice water for 2 min.

**Handgrip.** Maximal handgrip was maintained for 1 min.

**Histamine.** As suggested by Ginsburg et al.,9 2 hr before testing cinetidine (10 mg/kg) was administered orally, and 10 min before testing it was given intravenously (15 mg/kg) over 10 min. Histamine was then infused at an initial dose of 0.5 μg/kg/min for a 3 min period. If no chest pain or ischemic ECG changes occurred, a dose of 1 μg/kg/min was then administered over 3 min.

**Exercise testing.** Maximal treadmill exercise tests, by the modified Bruce protocol, were performed.

**Data analysis.** During noninvasive testing, a test was considered positive (indicative of coronary spasm) when ST segment elevation of 0.1 mV or more developed in leads with no pathologic Q waves. ST segment depression of 0.1 mV or more horizontal or downsloping was also considered to suggest spasm when it developed in the absence of any significant increase in rate-pressure product or in the presence of normal coronary arteries. During exercise, ST segment depression was interpreted as suggestive of spasm (positive test) only in patients with minor or no angiographic lesions. Angina alone was not considered a criterion for a positive test.

In patients who underwent repeated provocative testing, a “variable” response indicates that both positive and negative results occurred. A “consistent” response to a particular test (either positive or negative) indicates that the same result always occurred. Continuous data are presented as mean ± 1 SD. Sensitivity of different provocative tests was compared by chi-square analysis. A p value < .05 was considered indicative of a significant difference.

**Results**

A total of 324 provocative tests were carried out in 28 patients. Results of provocative tests are shown in tables 2 and 3 and summarized in figures 1 and 2.

**Ergonovine test.** Ergonovine provoked angina and ischemic ST segment shifts in 27 of 28 patients (96%) and chest pain alone in patient 22. Of a total of 74 tests performed in the 28 patients (2.6 tests/patient), 67 (90%) were positive. In all patients the ECG leads exhibiting ST shifts were the same during spontaneous and ergonovine-induced attacks. The ergonovine test was repeated at least twice in 26 patients. It was consistently negative in one (No. 22) and consistently positive in 22; of these 22, 16 always had ST segment elevation, four had ST segment depression, and two had either ST elevation or depression in the same ECG leads. In three patients (Nos. 19, 20 and 24) the response to ergonovine (300 μg) was variable: only one of three tests was positive (ST segment elevation) in two of these patients, and one of two tests was positive.
TABLE 2
Individual results of repeated provocative tests

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Study period (wk)</th>
<th>Ergonovine</th>
<th>Hyperventilation</th>
<th>Histamine</th>
</tr>
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<tr>
<td></td>
<td></td>
<td>ST/dose (µg)</td>
<td>ST segment</td>
<td>ST/dose (µg/kg)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>2</td>
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<tr>
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<td>6</td>
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<td>♦ 50</td>
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<td>♦ 200</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1/1</td>
<td>♦ 25</td>
<td>—</td>
</tr>
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<td>4</td>
<td>2</td>
<td>2/2</td>
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<td>♦ 100</td>
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<td>3/3</td>
<td>♦ 200</td>
<td>♦ 200</td>
</tr>
<tr>
<td>6</td>
<td>3^A</td>
<td>3/3</td>
<td>♦ 200</td>
<td>♦ 100</td>
</tr>
<tr>
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<td>2/2</td>
<td>♦ 50</td>
<td>—</td>
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<td>3/3</td>
<td>♦ 100</td>
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<td>28</td>
<td>4</td>
<td>3/3</td>
<td>♦ 100</td>
<td>♦ 100</td>
</tr>
</tbody>
</table>

P/p = number of positive tests/tests performed; RPP = heart rate-systolic blood pressure product; ♦ = ST elevation; ♦ = ST depression; 0 = no ST change (negative test); — = test not performed.

^A Patient had two “hot periods.”

(ST segment elevation) in the other. During the initial ergonovine test a positive response was obtained with a dose of 25 µg in one patient, with 50 µg in nine, with 100 µg in eight, with 200 µg in six, and with 300 µg in three. In 21 of the 26 patients who underwent repeated testing with ergonovine, the dose that provoked ischemic ECG changes was the same or varied only by one dose increment. During positive ergonovine tests, three patients had short salvos of ventricular tachycardia and two had sustained ventricular tachycardia that degenerated into ventricular fibrillation, which was promptly reverted by a precordial thump and intravenous nitrates in one case and by direct-current cardioversion in the other.

Hyperventilation test. Hyperventilation provoked angina and ischemic ST changes in 15 of the 28 patients (54%). Of 62 tests carried out in the 28 patients (2.2 tests/patient), 23 (37%) were positive. The test was done on at least two occasions in 24 patients (2.4 tests/patient). A consistently positive response was found in only four patients (ST segment elevation in all), while consistently negative results were obtained in 12. In the remaining eight patients the response was variable (ST segment elevation in seven, depression in one). Ischemic ST segment changes always developed within 3 min from the end of hyperventilation. One patient had nonsustained ventricular tachycardia during a positive test. Slight dizziness and paresthesia in both hands were present in all patients at the end of hyperventilation.

Histamine. Histamine was given to the last 15 patients with the exception of patient 22, who declined the test. In addition, patient 6 underwent the test during his second hot period (tables 1 and 2). Histamine
provoked angina and ischemic ECG changes in seven patients (47%; ST segment elevation in five, depression in two). Diagnostic ST shifts developed during the infusion of 1.0 μg/kg/min histamine in six patients and with 0.5 μg/kg/min in the remainder. In none of these patients did significant arterial hypotension occur during testing. Histamine-induced ECG changes occurred in the same leads in which spontaneous and ergonovine-induced attacks were documented. In one patient histamine provoked angina without ST changes and in seven it induced neither angina nor ST segment shifts. During the infusion of histamine four patients complained of headache, four others experienced a “hot flushing” in the face and neck, and five (33%) developed hypotension (70 to 80 mm Hg systolic), but this was transient (<15 min) and did not require treatment. No serious arrhythmia was observed during histamine testing.

**Cold pressor test and handgrip.** Only three patients had a positive cold pressor test (ST segment elevation in all) and this response was reproducible in one of them. Two patients (7%) had ST segment elevation and angina after the handgrip test, and these responses were reproducible in one. No serious side effects were observed, but most patients complained of severe arm and hand discomfort during the test.

**Exercise testing.** In 16 of the 28 patients (57%), exercise testing provoked angina and ST shifts. The response to exercise suggested coronary spasm in 13 patients (46% of the total population): six (all with significant coronary stenoses) had ST segment elevation and the other seven (with normal coronary arteries or nonsignificant stenoses) (tables 2 and 3) had ST segment depression. In the six patients with ST segment elevation, this response, which was suggestive of coronary spasm, was not observed during repeated exercise tests: in one of these patients further exercise tests were negative and in the other five only ST seg-
ment depression was observed. After repeated testing, two of the seven patients with normal coronary arteries and exercise-induced ST segment depression had a similar pattern of response, whereas five had negative tests at similar heart rate-blood pressure products. Two patients (Nos. 5 and 21) experienced nonsustained ventricular tachycardia during transient ST segment elevation and depression, respectively (table 2).

**Individual response to multiple provocative tests (figure 3).** At least two different provocative tests were positive in 23 of the 28 patients (82%). Three or more different stimuli induced coronary spasm in 11 patients (39%) and four or more different tests provoked spasm in 5 (18%) (tables 2 and 3). At least two episodes of transient myocardial ischemia were observed daily in 23 of the 28 patients while they were in the coronary care unit. In the remaining five (Nos. 7, 8, 11, 22, and 26), symptoms were less frequent than before admission, probably suggesting an increase in their threshold for spasm. All provocations were negative in patient 22 and only ergonovine triggered coronary spasm in patients 7, 8, 11, and 26. The relationships between the dose of ergonovine required to induce coronary spasm and the response of “less potent” stimuli is presented in figure 4.

**Coronary artery anatomy and results of provocative tests (figure 5).** Of the 28 patients, four had normal coronary arteries, 12 had nonsignificant stenoses, and 12 had significant stenoses. Spasm occurred at sites of significant lesions in 10 of the 28 patients (36%), at sites of 50% diameter reduction in four (14%), at sites of minor irregularities (10% to 30% reduction in diameter) in eight (29%), and in normal coronary arteries in the remaining six (21%). Four of the latter six patients (Nos. 14, 15, 22, and 24) had normal coronary arteries and two (Nos. 4 and 27) had significant stenoses of the

![Graph](https://example.com/graph.png)
FIGURE 2. Short-term reproducibility of results of provocative tests. Within 2 weeks the ergonovine test was repeated on at least two occasions in 26 patients, the hyperventilation test in 24, the exercise and handgrip tests in 23, and the cold pressor test in all (figures in brackets). For each provocative test, patients with a consistently positive response (one suggestive of coronary spasm) are represented by the solid bars; those with a variable response or a consistently negative response are indicated by the hatched and open columns, respectively.

right coronary artery, but spasm occurred in angiographically normal left anterior descending arteries.

The ergonovine test was positive in all 12 patients with significant stenoses (spasm developed at the site of the stenoses in 10 and in normal vessels in two) and in 15 of 16 with normal coronary arteries or nonsignificant stenoses. The hyperventilation test was positive in eight of 12 patients with significant lesions (67%) and in seven of 16 (44%) with nonsignificant stenoses. With hyperventilation spasm occurred in arteries with significant stenoses in six patients and at sites of nonsignificant stenoses in nine. The histamine test, performed in 15 patients, was positive in five of 11 (45%) without significant lesions and in two of four (50%) with significant stenoses. Stress testing results were positive, suggesting coronary spasm, in six of 12 patients (50%) with coronary artery disease and in seven of 16 (55%) with nonsignificant lesions or normal coronary arteriograms. Of three patients with a positive cold pressor test (ST segment elevation), two had coronary artery disease. The two patients with positive handgrip tests (ST segment elevation) had normal coronary arteries.

Discussion

Sensitivity and reproducibility of provocative tests. This study revealed that in patients with active vasospastic angina, ergonovine was the most potent of all the agents used in provoking coronary spasm. Hyperventilation, histamine, and exercise test were of intermedi-

FIGURE 4. Relationship between dose of ergonovine required to induce coronary spasm and results of multiple tests used in this study. The number of patients with ergonovine-induced coronary spasm at each dose level is indicated by the open bars. The hatched bars represent patients with ST shifts and angina (positive tests) after hyperventilation (HV), histamine (H), exercise testing (EX), the cold pressor test (CP), and handgrip (HG) at the different dose levels of ergonovine.

FIGURE 3. Individual responses to multiple provocative tests. In more than 80% of patients at least two different stimuli provoked coronary spasm. Three different agonist-receptor interactions (α-adrenergic, serotoninergic, and histaminergic) triggered spasm in the same individual in a sizeable proportion of patients. + ve = positive test(s), as defined in text.

FIGURE 5. Sensitivity of results of provocative tests in patients with significant coronary stenoses (CAD) and in patients with normal coronary arteries or nonsignificant stenoses (NCA). Positive tests with ST segment elevation are indicated by the hatched bars and ST segment depression by the open columns. Figures on top of bars indicate number of patients.
ate potency, while the cold pressor test and handgrip were less potent stimuli. Responses to provocative testing were similar in patients with normal coronary arteries or nonsignificant stenoses and in patients with significant coronary lesions.

The sensitivity to hyperventilation and histamine was lower than recently reported (approximately 70% to 80% and 90%, respectively, compared with ergonovine). With respect to hyperventilation, the spontaneous variability in the response to the test, different patient selection criteria, and the fact that a small number of patients have usually been included may account for the difference. It is also possible that, although all patients hyperventilated vigorously, the critical increase in pH necessary to induce spasm might not have been achieved in some of them. Since arterial pH was not monitored, we could have been unaware of this fact. For histamine, the available data are from only six selected patients with variant angina and therefore, as the authors of this report suggest, conclusions regarding the sensitivity of the histamine test for the identification of coronary spasm cannot be drawn from their study.

It is of interest that almost 50% of our patients had exercise-induced spasm. The sensitivity of exercise testing in the present study was higher than that found by others. This may reflect the criteria used here to define the presence of coronary spasm during the stress test. If only the criterion of ST segment elevation during the first exercise were used, the sensitivity would have been 21%, a figure consistent with other reports. Furthermore, since the spontaneous variability of the test result in patients with Prinzmetal's angina is high, repeated exercise testing probably recruited more patients with positive results than would a single test.

Results of repeated testing performed within a short period show that the reproducibility of the responses to the different stimuli parallels their potency as triggers of coronary arterial spasm. The fact that the response to stimuli of intermediate potency is highly variable in the same individual probably indicates that the threshold for spasm can vary dramatically.

Specific agonist-receptor interactions vs nonspecific local supersensitivity of the coronary arteries. Based on the observation that naturally occurring substances, when administered in pharmacologic doses, can provoke coronary arterial spasm in patients with variant angina, it has been postulated that supersensitivity of specific receptors and abnormal agonist-receptor interactions are mechanisms causing coronary spasm. Yasue et al. and Ricci et al., among others, have suggested that coronary spasm is mediated by α-adrenergic receptors. However, further studies failed to verify this hypothesis. No generalized autonomic (sympathetic or parasympathetic) abnormality was found to precede ischemic episodes in patients with variant angina. Furthermore, effective α-adrenergic blockade did not abolish episodes of coronary spasm in patients with Prinzmetal’s angina.

Ergonovine, the most potent stimulus for coronary spasm, has been found in animal and experiments in vitro to act mainly through serotonergic receptors. However, neither spontaneous nor induced coronary spasm is abolished by blockade of serotonergic receptors with ketanserin, thus suggesting that in man, the role of these receptors as mediators of spasm is uncertain.

Histamine, dopamine, ATP, and the parasympathetic nervous system have been shown to be involved in the production of spasm in some patients and thromboxane A2 has also been proposed as a cause of coronary spasm. Studies performed at our institution and others, however, did not confirm this hypothesis. The results obtained with both specific blockers and selective agonists suggest that triggers of spasm may be numerous, and that in patients with Prinzmetal’s angina particular coronary segments have an abnormal reactivity to different vasoconstrictor stimuli. Clinical studies have usually examined one or two stimuli that are capable of provoking coronary spasm. It has not been determined, however, whether spasm is triggered only by specific agonist-receptor interactions (perhaps different ones in different individuals) or whether there is nonspecific supersensitivity of the coronary arterial wall to a variety of stimuli.

The results of our study, in which diverse stimuli provoked spasm and electrocardiographic changes in the same leads within individuals, suggest that a local, nonspecific abnormal reactivity of the coronary vessels is the primary mechanism of spasm in these patients. Within individual patients spasm was induced after two or more vasoconstrictive stimuli in 82% and was observed after three or more stimuli in 39%. The fact that spasm was provoked within individuals by at least three different agonist-receptor interactions (α-adrenergic, histaminergic, serotonergic), as well as by stimuli such as hyperventilation, suggests that a nonspecific local abnormal sensitivity of the coronary arteries and not a supersensitivity of a specific class of receptors causes spasm.

Active vs passive mechanisms in the genesis of myocardial ischemia: role of coronary atherosclerosis. Since in a
clinical study of this nature coronary spasm cannot be documented angiographically on every occasion, concern may exist that some of the ischemic episodes triggered by provocative tests that may lower systemic blood pressure or induce myocardial arteriolar vasodilatation do not result from coronary arterial spasm but from any of several other possible mechanisms. It has been shown that changes in vasomotor tone, even within the physiologic range, at the level of a significant stenosis may dramatically influence coronary blood flow distal to the stenosis (dynamic stenoses). 

It has been proposed that coronary spasm is the result of normal vasomotion at sites of pliable atheromatous stenoses that, acting as "levers," magnify the effects of physiologic smooth muscle contraction on luminal diameter. Furthermore, the distal dilatation that can be caused by exercise, handgrip, and histamine can increase the resistance in a significant compliant stenosis. Increased flow through a stenosis may result in excessive pressure loss at the level of stenosis and may lead to passive collapse. For this mechanism to be in effect, however, the presence of both significant coronary stenoses and a large increase in coronary flow or a marked drop in aortic pressure is necessary. Therefore, passive closure of the vessel would not explain the ischemic episodes triggered by provocative tests in patients without significant lesions (60% of patients in this study). In the remaining 40%, those with significant coronary stenoses, the possibility that stimuli that lowered systemic blood pressure, increased coronary flow, or both, might have produced ischemia by mechanisms different than coronary spasm cannot be ruled out. However, our results indicate that coronary spasm was indeed the cause of ischemia associated with provocative testing in patients without significant lesions as well as in patients with critical stenoses, for the following reasons:

1. No differences were found in the response to diverse vasoconstrictive stimuli in patients with significant coronary lesions and those with normal arteries or minimal coronary stenoses.

2. Patients 4, 8, and 27, all with significant atherosclerotic lesions in one coronary artery, had neither angina nor ischemic ST segment shifts during maximal stress testing. This indicates that although "anatomically significant," these obstructions did not provoke myocardial ischemia even in the presence of a marked increase in oxygen demand. Moreover, spasm was observed in arteries that were angiographically normal in two patients with significant single-vessel disease (blocked right coronary arteries), thus providing evidence that in these individuals ischemia did not arise from stenotic vessels.

3. In this selected group of patients with vasospastic angina (with or without coronary lesions), ischemic episodes triggered by stimuli that may have systemic effects (histamine, handgrip, cold pressor) were similar to those provoked by ergonovine. Furthermore, in none of the patients with positive histamine tests were marked drops in systemic arterial pressure observed. Conversely, ischemic ECG changes and angina were not observed in five patients (three with critical stenoses) who experienced a significant fall in systolic pressure during histamine testing.

Our data are in agreement with those of Freedman et al., who showed that patients with Prinzmetal's angina have an increased sensitivity to coronary vasoconstrictors at the level of organic stenoses, and with findings by Hill et al., who suggested that a localized disorder in coronary vasomotion is present in patients with coronary spasm, and that this is not limited to constriction but also involves increased dilation in response to nitroglycerin.

The cause of the nonspecific local supersensitivity of the coronary arteries of patients with variant angina is still speculative. Coronary atherosclerosis has been suggested to be the "localizing factor" for spasm. Recent experimental evidence suggests that the hypercontractility of the arterial wall might be associated with the atherosclerotic process itself. A number of events that are linked to the formation of a plaque have been proposed as local triggers of spasm: endothelial injury, increased density of receptors mediating smooth muscle constriction, and release of vasoactive products by leucocytes and platelets. A series of clinical observations and experimental data, however, indicate that this issue remains controversial. Symptoms and a positive response to ergonovine in patients with variant angina may persist during long-term follow-up, suggesting that acute events at the level of the atherosclerotic plaque are unlikely to be the only cause of a chronic hyperreactivity of the coronary arteries. In addition, spasm has been documented in normal coronary arteries. It has also been suggested that factors other than atherosclerosis play a role, such as intimal dysplasia, involvement of multiple receptors, local vascular nerve lesions, increased population of adventitial mast cells, and mechanisms beyond the level of interaction between agonists and receptors.

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