Spontaneous Coronary Artery Spasm in Variant Angina Is Caused by A Local Hyperreactivity to a Generalized Constrictor Stimulus

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To assess whether spontaneous coronary artery spasm in patients with variant angina results from local coronary hyperreactivity to a generalized constrictor stimulus or from a stimulus generated only at the site of the hyperreactive segment, the behavior of spastic and nonspastic coronary segments was studied in six patients with variant angina in whom focal coronary spasm developed spontaneously during cardiac catheterization. None of the patients had critical (>50% luminal diameter reduction) organic coronary stenoses. Coronary diameters were measured by computerized quantitative arteriography during control, spontaneous spasm and ergonovine-induced spasm and after intracoronary nitrates were given.

During spontaneous spasm, the luminal diameter of spastic and both proximal and distal nonspastic coronary segments was significantly reduced from control values, 64.2%, 13.2% and 14.8%, respectively. Average diameter reduction of unrelated arteries was 12.3%. Ergonovine, which was also administered to four patients, provoked focal spasm at the same site as spontaneous spasm. During intravenous ergonovine, luminal diameter of spastic segments was reduced by 91.5%, that of nonspastic proximal segments by 17.8% and that of nonspastic distal segments by 11.5%. Luminal diameter of unrelated arteries during ergonovine-induced spasm was reduced by 17.7%. Constriction of spastic segments was greater during ergonovine-induced spasm (p < 0.05), whereas the extent of diameter reduction of nonspastic segments was not significantly different during spontaneous spasm and ergonovine-induced spasm. Intracoronary isosorbide dinitrate dilated spastic and nonspastic coronary segments to a similar extent from control (20.7%, 18% and 16.5%, respectively; p = NS).

This study demonstrates that spontaneous focal coronary spasm in variant angina results from a local exaggerated coronary constrictor response to a generalized stimulus that produces only mild constriction in other coronary segments.

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Although coronary artery spasm was considered to be a proved hypothesis more than a decade ago (1), its causes are still incompletely understood. We (2) have shown that ergonovine causes focal coronary artery spasm in patients with variant angina by a direct local coronary effect while producing only mild constriction on other segments of the spastic artery and adjacent branches. This local hyperreactivity in variant angina does not appear to be specific for a single type of agonist-receptor interaction, because spasm can be induced by a variety of stimuli acting through different receptors (3). It is not known, however, whether coronary spasm that occurs spontaneously also results from a local coronary hyperreactivity to a generalized constrictor stimulus affecting the coronary arteries diffusely or just from a localized stimulus generated at the site of the hyperreactive segment. To address this question we analyzed the behavior of spastic and nonspastic coronary artery segments during episodes of spontaneous coronary spasm observed during angiography in six patients with variant angina.

Methods

Study patients. From 1982 to 1987, 58 patients with the syndrome of Prinzmetal's variant angina underwent cardiac catheterization in our institution. Of these, six (five men, one woman; mean age 50 ± 7 years) developed coronary spasm spontaneously during cardiac catheterization and are the
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MECHANISMS OF SPONTANEOUS CORONARY SPASM IN VARIANT ANGINA

Table 1. Clinical and Angiographic Characteristics of Six Patients With Variant Angina

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Type</th>
<th>Onset (mo)</th>
<th>Basal</th>
<th>During Spontaneous Angina</th>
<th>During Ergonovine*</th>
<th>Baseline Coronary Angiography (% stenosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49F</td>
<td>E+R</td>
<td></td>
<td>12</td>
<td>Normal</td>
<td>ST ↑ V₁-V₃</td>
<td>ST ↑ V₁-V₃</td>
<td>LAD 35%</td>
</tr>
<tr>
<td>2</td>
<td>54M</td>
<td>R</td>
<td></td>
<td>72</td>
<td>Normal</td>
<td>ST ↑ II,III,aVF</td>
<td>ST ↑ II,III,aVF</td>
<td>LCx 30%; RCA 14%</td>
</tr>
<tr>
<td>3</td>
<td>55M</td>
<td>R</td>
<td></td>
<td>6</td>
<td>Normal</td>
<td>ST ↑ II,III,aVF</td>
<td>ST ↑ II,III,aVF</td>
<td>LAD 12%; RCA 21%</td>
</tr>
<tr>
<td>4</td>
<td>47M</td>
<td>R</td>
<td></td>
<td>4</td>
<td>Normal</td>
<td>ST ↑ II,III,aVF</td>
<td>ST ↑ II,III,aVF</td>
<td>LCx 30%; RCA 42%</td>
</tr>
<tr>
<td>5</td>
<td>58M</td>
<td>R</td>
<td></td>
<td>24</td>
<td>Normal</td>
<td>ST ↑ V₂-V₄</td>
<td>ST ↑ V₂-V₄</td>
<td>LAD 11%; RCA 40%</td>
</tr>
<tr>
<td>6</td>
<td>38M</td>
<td>R</td>
<td></td>
<td>7</td>
<td>Normal</td>
<td>ST ↓ V₂-V₄</td>
<td>ST ↓ V₂-V₄</td>
<td>LMS 40%; LAD 32%</td>
</tr>
</tbody>
</table>

*Performed in the noninvasive laboratory. E = effort; ECG = electrocardiogram; F = female; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LMS = left main stem; M = male; R = rest; RCA = right coronary artery; ST = ST segment; ↓ = depression; ↑ = elevation.

subject of this report. All six patients had a history typical of variant angina, with anginal episodes at rest, usually at night and in the early morning hours, but with preserved exercise capacity. Anginal episodes were associated with transient ST segment elevation (five patients) or depression (one patient), documented by ambulatory electrocardiographic (ECG) monitoring. Since the onset of the syndrome of variant angina, these patients had had periods of spontaneous waxing and waning of the disease. Although at admission all patients were in an active phase of their variant angina, with one to eight anginal episodes (mean 2.8 episodes/patient) in the week preceding admission, anginal attacks were usually short-lasting and resolved spontaneously within 3 min or were promptly relieved by sublingual nitrates in all cases. The clinical and angiographic characteristics of the patients are summarized in Table 1.

Ergonovine provocative testing. Each patient underwent provocative testing in the noninvasive laboratory with incremental doses of ergonovine and 12 lead ECG monitoring, using a protocol described in detail elsewhere (3). During intravenous ergonovine administration, all patients had their usual anginal pain, which was associated with marked ST segment elevation in five patients and ST segment depression in one patient, thus reproducing findings during spontaneous anginal episodes (Table 1). Ergonovine-induced myocardial ischemia was completely reversed within 60 s by intravenous isosorbide dinitrate.

Cardiac catheterization. Every patient gave written informed consent for coronary arteriography and administration of ergonovine during cardiac catheterization. The study protocol was approved by the Hammersmith Hospital Ethics Committee.

Use of antianginal medications was discontinued at least 48 h before cardiac catheterization, with the exception of sublingual nitrates, which were administered as needed. Patients were studied in the fasting state, received no premedication and had not smoked or taken sublingual nitrates in the 6 h preceding coronary arteriography. The Judkins technique was used in all patients. Baseline diagnostic (control) coronary angiograms were obtained in Patients 1, 2, 3, 4 and 5. In these five patients chest pain developed spontaneously 1 to 3 min after baseline coronary angiography and was associated with ischemic ST segment changes in four (Patients 1 through 4). Angiography of the appropriate coronary artery was immediately performed and demonstrated nonocclusive focal coronary spasm in all cases. The coronary artery to receive an injection during spontaneous chest pain was selected on the basis of either ECG changes observed during monitoring at angiography (Patients 1 through 4) or the result of the ergonovine test previously performed in the noninvasive laboratory (Patient 5). In Patient 6, ischemic ST segment changes in the anterior leads and chest pain developed spontaneously before diagnostic coronary angiography was performed. Left coronary arteriography revealed focal coronary spasm of both the left anterior descending coronary artery and left main stem. Coronary angiography was repeated without therapy in this patient within 1 week of the previous study to obtain further information for clinical management and this second coronary arteriogram was used as control. Patients were not kept in the catheterization laboratory until spontaneous coronary spasm developed. As described earlier, spasm developed by chance 1 to 3 min after completion of baseline coronary angiograms in Patients 1 to 5 and before baseline angiography in Patient 6.

Ergonovine testing during cardiac catheterization. In four patients (Patients 1, 3, 4 and 5), coronary spasm resolved spontaneously within 60 s. These four patients then underwent provocative testing with incremental doses of intravenous ergonovine (3) during cardiac catheterization, which provoked focal spasm in all four. Ergonovine-induced spasm was promptly reversed by intracoronary isosorbide dinitrate (1 to 3 mg) in all four cases. In Patient 2, in whom spasm did not resolve spontaneously within 1 min, and in Patient 6, who had spasm of both the left anterior descending artery and left main stem, intracoronary isosorbide dinitrate (2 mg) was immediately given, with prompt resolution of spasm in both cases. These two patients were not administered ergonovine during cardiac catheterization. Angiograms were also obtained during ergonovine testing in Patients 1, 3, 4.
Coronary segments considered for measurement are schematically shown in Figure 1. In the spastic vessel, the spastic segment as well as one proximal and one distal nonspastic segment were analyzed. Proximal and distal coronary segments of the nonspastic circumflex artery were also analyzed when spasm developed in the left anterior descending coronary artery. Narrowed segments that did not change in diameter after administration of intracoronary nitrates at the end of the study were considered “fixed” stenoses.

Data analysis. Minimal luminal diameter of spastic and nonspastic coronary segments at baseline angiography (in the absence of chest pain or ECG changes), during spontaneous spasm and ergonovine-induced spasm and after administration of nitrates was measured in millimeters. Results are expressed as mean values ± 1 SD of the absolute values of the minimal luminal diameter at the site of spastic and nonspastic segments. Changes in coronary caliber of spastic and nonspastic segments are expressed as percent change relative to control values. Paired and unpaired t-tests were used, as appropriate, to analyze changes in luminal diameter. A p value < 0.05 was considered statistically significant.

Results

Baseline angiography. In no cases were severe (>50% luminal diameter reduction) coronary atheromatous obstructions observed during baseline angiography, although patients had organic coronary stenoses ranging from 11% to 42% diameter reduction (Tables 1 and 2). During control arteriography, the luminal diameter of segments that developed spasm was 2.19 ± 0.49 mm, whereas luminal diameters of proximal and distal nonspastic segments were 3.39 ± 0.74 and 2.79 ± 0.43 mm, respectively (Tables 3 and 4).

Spontaneous coronary spasm. Angina and ischemic ST segment changes that occurred in association with coronary spasm during cardiac catheterization developed when no catheter manipulations or contrast injections were being carried out. Spontaneous nonocclusive focal spasm developed at the site of mild atheromatous coronary stenoses.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Spastic Segment (% fixed stenosis)</th>
<th>Spontaneous Spasm</th>
<th>Ergonovine-induced Spasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Proximal LAD (35%)</td>
<td>ST ↑ V₁-V₁₀</td>
<td>ST ↑ V₁-V₁₀</td>
</tr>
<tr>
<td>2</td>
<td>Mid-RCA (14%)</td>
<td>ST ↑ II,III,AVF</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>Mid-RCA (21%)</td>
<td>ST ↑ II,III,AVF</td>
<td>ST ↑ II,III,AVF</td>
</tr>
<tr>
<td>4</td>
<td>Mid-RCA (42%)</td>
<td>ST ↑ II,III,AVF</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>Mid-LAD (11%)</td>
<td>Nil</td>
<td>ST ↑ II,III,AVF</td>
</tr>
<tr>
<td>6</td>
<td>Proximal LAD (37%); and LMS (40%)</td>
<td>ST ↑ V₁-V₁₀</td>
<td>ND</td>
</tr>
</tbody>
</table>

*Mild chest discomfort; + = present; ND = ergonovine test not done; other abbreviations and symbols as in Table 1.
Table 3. Changes in Luminal Diameter of Spastic Coronary Segments During Spontaneous Spasm, Ergonovine Induced Coronary Spasm and After Intracoronary Nitrates in Six Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Control (mm)</th>
<th>Spontaneous Spasm mm</th>
<th>% Change</th>
<th>Ergonovine mm</th>
<th>% Change</th>
<th>Isosorbide Dinitrate mm</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>0.91</td>
<td>-55</td>
<td>0</td>
<td>-100</td>
<td>2.14</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>3.07</td>
<td>0.67</td>
<td>-78</td>
<td>ND</td>
<td>ND</td>
<td>3.67</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>2.3</td>
<td>0.46</td>
<td>-80</td>
<td>0</td>
<td>-100</td>
<td>2.48</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>1.57</td>
<td>0.98</td>
<td>-38</td>
<td>0.54</td>
<td>-66</td>
<td>2.64</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>2.1</td>
<td>1.03</td>
<td>-51</td>
<td>ND</td>
<td>ND</td>
<td>2.23</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>2.1</td>
<td>0.35</td>
<td>-83</td>
<td>ND</td>
<td>ND</td>
<td>2.45</td>
<td>17</td>
</tr>
<tr>
<td>Mean</td>
<td>2.19</td>
<td>0.73</td>
<td>-64.17</td>
<td>0.14</td>
<td>-91.50</td>
<td>2.60</td>
<td>20.67</td>
</tr>
<tr>
<td>SD</td>
<td>0.49</td>
<td>0.28</td>
<td>18.65</td>
<td>0.27</td>
<td>17.00</td>
<td>0.55</td>
<td>23.86</td>
</tr>
</tbody>
</table>

Negative values indicate percent reduction of coronary luminal diameter. ND = not done; SD = standard deviation.

(range 11% to 42% diameter reduction) in all cases. However, fixed stenoses of a similar severity were also present in coronary segments that did not develop spasm (Table 1). Spontaneous spasm occurred in the left anterior descending coronary artery in Patients 1 and 5, in the right coronary artery in Patients 2, 3 and 4 and simultaneously in both the left anterior descending artery and left main stem (60% luminal diameter reduction) in Patient 6 (Table 2).

Spontaneous coronary spasm was associated with angina and transient ischemic ST segment changes in five patients and with only minor chest discomfort in 1 patient (Patient 5) (Table 2). Myocardial ischemia subsided spontaneously within 60 s in four patients and resolved immediately after intracoronary isosorbide dinitrate (2 mg) in two. Angina during spontaneous spasm was associated with ST segment elevation in Patients 2, 3 and 4 and with ST segment depression in Patients 1 and 4. Patient 5 had mild chest discomfort and no ischemic ST segment changes (Table 2).

**Ergonovine-induced spasm.** Ergonovine, which was administered to four patients during cardiac catheterization, provoked occlusive focal spasm at the same site as spontaneous coronary spasm in all four cases (Table 2). Ergonovine-induced spasm was associated with angina and ST segment elevation in all four patients (Table 2); prompt resolution of ergonovine-induced spasm followed the intracoronary administration of isosorbide dinitrate in all cases.

**Behavior of spastic segments.** During spontaneous spasm mean coronary diameter of spastic segments was reduced by 64.2 ± 18.6% from control (from 2.19 ± 0.49 to 0.73 ± 0.28 mm; p < 0.001) (Table 3, Fig. 2 and 3). The degree of luminal diameter reduction observed at the site of spastic segments during spontaneous spasm significantly exceeded that predicted by the geometric theory: 64.2 ± 18.6% versus 41 ± 12%, respectively (p < 0.05).

During *ergonovine-induced spasm*, mean diameter of spastic segments was reduced by 91.5 ± 17% (from 1.99 mm [mean control value in the four patients who received ergonovine] to 0.14 mm; p < 0.001). The extent of luminal reduction was significantly greater (p = 0.01) after administration of ergonovine compared with that during spontaneous spasm.

**Behavior of nonspastic segments.** Eighteen nonspastic segments were analyzed: two in each spastic vessel and another six (three proximal and three distal) in the circumflex arteries of the three patients in whom spasm of the left anterior descending coronary artery developed (Fig. 1).

**Figure 2.** Intraluminal coronary diameter of all spastic segments (A), proximal nonspastic segments (B) and distal nonspastic segments (C). Measurements in individual patients were obtained during control, spontaneous (Spont) spasm and ergonovine-induced (Ergo) spasm and after administration of intracoronary isosorbide dinitrate (ISDN).
Figure 3. Percent change (average values) of coronary intraluminal diameter of spastic and nonspastic coronary segments during spontaneous spasm and ergonovine-induced spasm and after administration of intracoronary nitrates.

During spontaneous spasm a diffuse and mild coronary constriction was observed in the nonspastic segments. Compared with control, luminal diameter of proximal nonspastic segments was reduced by 13.2 ± 7.5% (from 3.39 ± 0.74 to 2.99 ± 0.88 mm; p < 0.01). Diameter of distal nonspastic segments was reduced by 14.8 ± 11% (from 2.79 ± 0.43 to 2.38 ± 0.50 mm; p = 0.03) (Table 4, Fig. 2 and 3). The degree of coronary constriction observed during spontaneous spasm was not significantly different in nonspastic segments of the spastic vessel compared with segments located in unrelated arteries: 15.3 ± 8% versus 12.3 ± 9% reduction in caliber, respectively (p = 0.46). Moreover, the extent of constriction of proximal and distal nonspastic segments was also similar (p = 0.74) (Table 4, Fig. 3). Changes in caliber observed during spontaneous coronary spasm was not significantly different in nonspastic segments with obstructions of 12% to 40% showed a 14.7 ± 9% reduction (p = 0.76).

During ergonovine-induced spasm, the extent of luminal diameter reduction of proximal nonspastic segments from control was not significantly different from that observed during spontaneous spasm: 17.7 ± 9.8% versus 13.2 ± 7.5%; p = 0.52 (Table 4, Fig. 2 and 3). Luminal diameter of unrelated arteries was reduced by 17.75 ± 9% during ergonovine-induced spasm.

Effects of intracoronary nitrates on spastic and nonspastic segments. Intracoronary isosorbide dinitrate was administered to all patients to relieve either spontaneous (two patients) or ergonovine-induced spasm (four patients). After intracoronary isosorbide dinitrate, the coronary diameter of spastic segments increased by 20.7 ± 23.9% compared with control (from 2.19 ± 0.49 to 2.60 ± 0.55 mm) (Table 3, Fig. 2 and 3). Coronary diameter of proximal and distal nonspastic segments increased by 18 ± 13.5% and 16.5 ± 12%, respectively (Table 4, Fig. 3). Compared with control, differences observed between the coronary dilation of spastic and nonspastic segments after nitrate administration were not statistically significant (Fig. 3). All patients completed the study without occurrence of any untoward cardiac events.

Discussion

Mild, generalized vasoconstriction in the presence of severe focal spasm in variant angina. In this study we have documented, using computerized coronary arteriography, that in addition to the focal and exaggerated vasoconstriction that develops in the spastic segments during spontaneous spasm, a mild and diffuse vasoconstriction occurs in the remaining segments of the spastic artery and in the nonspastic coronary arteries in patients with Prinzmetal's variant angina. Ergonovine-provoked focal spasm at the same site as spontaneous spasm but the extent of luminal narrowing

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Control (mm)</th>
<th>Spontaneous Spasm</th>
<th>Ergonovine</th>
<th>Isosorbide Dinitrate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Change</td>
<td>mm</td>
<td>mm</td>
<td>mm</td>
</tr>
<tr>
<td>1</td>
<td>3.24</td>
<td>2.7</td>
<td>-17</td>
<td>2.25</td>
</tr>
<tr>
<td>2</td>
<td>3.35</td>
<td>2.9</td>
<td>-14</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>3.44</td>
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<td>3.24</td>
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<td>4</td>
<td>2.86</td>
<td>2.67</td>
<td>-7</td>
<td>2.37</td>
</tr>
<tr>
<td>5</td>
<td>4.78</td>
<td>4.73</td>
<td>-2</td>
<td>3.92</td>
</tr>
<tr>
<td>6</td>
<td>2.68</td>
<td>2.26</td>
<td>-16</td>
<td>ND</td>
</tr>
<tr>
<td>Mean</td>
<td>3.39</td>
<td>2.99</td>
<td>-13.17</td>
<td>2.95</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Control (mm)</th>
<th>Spontaneous Spasm</th>
<th>Ergonovine</th>
<th>Isosorbide Dinitrate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Change</td>
<td>mm</td>
<td>mm</td>
<td>mm</td>
</tr>
<tr>
<td>1</td>
<td>2.22</td>
<td>1.9</td>
<td>-15</td>
<td>2.02</td>
</tr>
<tr>
<td>2</td>
<td>3.08</td>
<td>2.45</td>
<td>-20</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
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<td>2.42</td>
<td>-26</td>
<td>*</td>
</tr>
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</tr>
<tr>
<td>6</td>
<td>2.46</td>
<td>1.87</td>
<td>-24</td>
<td>ND</td>
</tr>
<tr>
<td>Mean</td>
<td>3.39</td>
<td>2.99</td>
<td>-13.17</td>
<td>2.95</td>
</tr>
</tbody>
</table>

*We were unable to measure segments distal to occlusive spasm. Abbreviations as in Table 3.
induced by this agent was greater, probably reflecting that
different stimuli may elicit different degrees of response from
the hyperreactive segment. Nonspastic segments during
both spontaneous spasm and ergonovine-induced spasm,
however, showed similar degrees of vasoconstriction.

Our findings provide the first objective demonstration
that spontaneous coronary spasm in patients with variant
angina results from a local exaggerated constrictor response
to a generalized stimulus, which produces only mild con-
striction in both the remaining segments of the spastic vessel
and in the nonspastic coronary arteries. The findings in our
study are in agreement with the observations of Curry et al.
(4), who noted mild, generalized epicardial coronary dia-
ter reduction in some nonspastic segments during both
spontaneous and ergonovine-induced spasm in patients with
variant angina. These investigators, however, did not quanti-
fy the degree of coronary constriction that developed in
spastic and nonspastic segments.

Mechanism of coronary spasm in variant angina. Al-
though the nature of the generalized vasoconstrictor stimu-
lus is unknown, the demonstration of its effect on hyperre-
active coronary segments and nonspastic arteries is im-
portant for the understanding of the mechanisms of coro-
nary spasm in variant angina. Indeed, for spontaneous
 coronary spasm to develop, both a hyperreactive coronary
segment and a generalized constrictor stimulus affecting all
coronary vessels appear to be necessary. We (3) and others
(5-10) have shown that, in patients with variant angina, a
large variety of different stimuli, and not a specific stimulus
only, can produce coronary constriction to a degree similar
to that produced in this study, thus indicating that a local
non-specific coronary hyperreactivity to different constrict-
ors is of paramount importance in the genesis of spasm in
variant angina. This may explain why theories that propose
specific receptor-agonist interactions involving parasympa-
thetic (6), alpha-adrenergic (11-13), histaminergic (14) and
serotonergic (15) mechanisms or thromboxane A2-prostacy-
clin imbalance (16) as the cause of coronary spasm could not
be confirmed (15,17-24). It also explains why, although
specific antagonists fail to prevent spasm (15,17-24), drugs
that nonspecifically reduce the constrictor response of the
coronary smooth muscle, such as nitrates and calcium
antagonists, are effective for treatment of variant angina
(25-28).

Because constrictor stimuli are often present during or-
dinary daily activities, changes of the “threshold” for spasm
at the site of the hyperreactive segments are likely to play a
major role in determining the frequency and severity of
ischemic episodes in patients with variant angina. We pre-
viously suggested that a variable susceptibility to spasm
is present in variant angina because the dose of ergonovine
required to provoke spasm in the same patient at different
times is extremely variable (29). A variable susceptibility to
spasm, within individuals, is also consistent with the fre-
quent observation of active phases alternating with quies-
cent periods or long-lasting remissions (30,31). During a
quiescent period or during treatment with calcium antago-
nists, spasm can sometimes be triggered by potent stimuli
such as ergonovine; in most patients, however, the er-
gonovine test also may become negative transiently or
persistently (30-33).

This study also demonstrates that focal coronary spasm
does not result from the amplification of physiologic vaso-
constriction at sites of subintimal plaques as proposed by
MacAlpin (“geometric theory”) (34). Although focal spasm
occurred consistently in association with atheromatous cor-

nary narrowings, in our patients during spontaneous coro-
nary spasm and as shown by Freedman et al. (35) during
ergonovine challenge, the degree of vasoconstriction ob-

served at the spastic segments far exceeded that predicted
by the geometric theory, confirming the presence of a local
coronary hyperreactivity. This is consistent with our find-
ings during provoked coronary spasm (2,3) and also with
recent observations of recurrence of spasm at the same
arterial site over prolonged periods (36).

Local coronary factors contributing to segmental spasm.
The nature of the local coronary alteration that makes a
particular coronary segment chronically hyperreactive to
stimuli that cause only mild constriction in the other coro-
nary arteries is not known. Certainly the syndrome of
variant angina cannot be explained simply by the presence
of an atheromatous plaque. Plaque rupture or fissuring is
unlikely to be the cause of spontaneous spasm in the chronic
forms of variant angina because this disease often remains
relatively stable for months (30,37), as in the case of the six
patients described in this study. Endothelial dysfunction
caused only by a raised plaque is also an unlikely cause of
local hyperreactivity because raised plaques were found to
cover as much as 20% to 30% of the surface of epicardial
coronary arteries of normal individuals who died in acci-
dents (38). Furthermore, a local deficit of endothelium-
derived relaxing factor (39) probably does not play a role in
the genesis of variant angina; in experimental animals endo-
thelial denudation alone was found to be insufficient to
trigger coronary spasm (40). Increased numbers of specific
receptors in certain segments of the coronary arteries also
seems unlikely, because the spastic segments are hyperre-
active to a large number of agonists (5). A postjunctional
supersensitivity (41) of local arterial smooth muscle appears
as a more attractive hypothesis.

The finding in our patients that the dilator response to
intracoronary nitrates was similar in spastic and nonspastic
coronary segments is compatible with an abnormality con-

fined to the constrictor response. The contrasting conclu-
sions reached by Hill et al. (42), who observed that in
patients with variant angina coronary segments involved in
coronary spasm exhibited an exaggerated response to nitro-
glycerin, may be explained by an increased basal tone of the spastic segments in their patients.

Conclusions. Spontaneous focal coronary spasm in patients with variant angina results from the interaction between a local coronary hyperreactivity, probably involving the smooth muscle locally, and the presence of a generalized stimulus that affects all coronary arteries, provoking complete vessel occlusion only at the site of the local hyperreactivity and only mild constriction in nonspastic arteries. Animal models (40,43) might provide insight into the basic mechanisms potentially responsible for the local coronary hyperreactivity in variant angina.

Although focal coronary spasm as documented in this study is by far the most common clinical presentation of spasm in variant angina, the occasional observation of severe diffuse constriction involving all epicardial coronary arteries (44,45) may suggest that the interaction between the local hyperreactivity and constrictor stimuli may vary from patient to patient.

References


