Coronary Vasomotor Effects of Serotonin in Patients With Angina
Relation to Coronary Stenosis Morphology

Dimitris Tousoulis, MD; Graham Davies, MD, FRCP; Eugene McFadden, MRCP, FESC; John Clarke, MD, PhD, MRCP; Juan Carlos Kaski, MD; Attilio Maseri, MD, FRCP

Background. Previous experimental studies have shown that the effect of serotonin on a coronary stenosis depends on whether that stenosis is compliant or fixed. However, the relation between coronary stenosis morphology and the response to serotonin in patients with angina is not known.

Methods and Results. Using computerized quantitative coronary angiography, we studied the effects of intracoronary infusion of serotonin on 38 coronary stenoses of different morphologies (concentric, eccentric, complicated) in 11 patients with stable angina and 4 with variant angina. In response to the maximum infused concentration of serotonin, 100% of complicated stenoses and 50% of concentric stenoses constricted by ≥20% (P<.05). The magnitude of constriction was greater at eccentric stenoses (32.08±4.1%) than concentric stenoses (15.68±2.8%, P<.05) and greater in complicated stenoses (57.69±7.6%, P<.05) than eccentric stenoses. At complicated stenoses, the constriction was greater (0.85±0.16 mm, P<.05) than at the adjacent reference segments (0.42±0.12 mm). It was similar to the reference segment for both concentric and eccentric stenoses. The constriction at the stenosis was greater for irregular (complicated) lesions than for smooth (concentric and eccentric) lesions in both patients with stable (51.8±7.3% versus 22.5±4.1%, P<.001) and those with variant (77±17% versus 28.2±8.1%, P<.05) angina. There was a weak correlation (r=.39) of magnitude of constriction with stenosis length but not with baseline stenosis severity (minimum diameter).

Conclusions. In these patients, the magnitude of the vasoconstrictor response to serotonin at the site of an atheromatous coronary plaque depends on the morphological characteristics of the plaque and is more closely related to irregular contour than stenosis severity or length. This relation suggests that variations in receptor type or density in or the smooth muscle cell response to stimulation may determine the response to locally released serotonin in patients with coronary disease. (Circulation. 1993;88[part 1]:1518-1526.)

Key Words • angina • stenosis • serotonin

Evidence suggests that the obstruction associated with a coronary artery stenosis is often dynamic rather than fixed.1 A 10% circumferential shortening of the normal wall may lead to a greater change in luminal caliber at the site of an eccentric plaque than at the site of a concentric plaque.2-3 Furthermore, coronary stenosis morphology may be an important factor determining the degree of vasomotor response to stimulation.4 Previous studies in animals have shown that the intracoronary activation of platelets may contribute to or cause myocardial ischemia both by causing mechanical obstruction of the arterial lumen and by releasing potent vasoconstrictor substances such as serotonin.5-13 and recent studies support a role for these mechanisms in humans.14-17 Experimental studies18 show that the effects of serotonin differ depending on whether the stenosis is compliant or fixed. There is little information, however, on the relation between coronary stenosis morphology and the vasomotor response to serotonin in patients with angina syndromes.

To study the vasomotor effects of serotonin and their relation to coronary stenosis morphology, we used quantitative angiography to examine the effect of intracoronary serotonin infusion on coronary luminal diameter at the site of concentric, eccentric, and complicated lesions in patients with chronic stable angina and patients with variant angina.

Methods

Patients
Fifteen patients admitted for routine cardiac catheterization were studied. The study protocol was approved by the Research Ethics Committee of the Hammersmith Hospital, and written informed consent was obtained from all patients. Regular medication for angina was discontinued at least 24 hours before catheterization. All patients continued to take aspirin (100 to 300 mg/d). Patients were allowed to use sublingual nitroglycerin as needed, but no study was performed within 3 hours of its administration.

Eleven patients (8 men and 3 women) 48.3±10 years old (range, 34 to 68 years) had chronic stable angina and a positive exercise test result (≥0.1 mV ST segment

Received November 5, 1992; revision accepted June 8, 1993.
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TABLE 1. Clinical and Angiographic Characteristics of Patients With Stable and Variant Angina

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>Type of Angina</th>
<th>Stenosis Location</th>
<th>Stenosis Morphology and Severity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>M</td>
<td>Stable</td>
<td>LCx</td>
<td>CO (23.5)</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>M</td>
<td>Stable</td>
<td>LCx</td>
<td>EC (28.5), CM (59.7)</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>M</td>
<td>Stable</td>
<td>RCA</td>
<td>CO (28.2), CO (30.2), EC (25.3)</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>M</td>
<td>Stable</td>
<td>LAD</td>
<td>CM (20.1)</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>M</td>
<td>Stable</td>
<td>RCA</td>
<td>CM (29.0), CM (50.0)</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>F</td>
<td>Stable</td>
<td>LCx</td>
<td>CO (30.9), EC (50.0)</td>
</tr>
<tr>
<td>7</td>
<td>34</td>
<td>M</td>
<td>Stable</td>
<td>LAD</td>
<td>CM (20.0)</td>
</tr>
<tr>
<td>8</td>
<td>68</td>
<td>F</td>
<td>Stable</td>
<td>LAD</td>
<td>EC (27.7)</td>
</tr>
<tr>
<td>9</td>
<td>37</td>
<td>M</td>
<td>Stable</td>
<td>LAD</td>
<td>CO (34.8), EC (26.0), CM (21.8)</td>
</tr>
<tr>
<td>10</td>
<td>48</td>
<td>M</td>
<td>Stable</td>
<td>RCA</td>
<td>CM (35.8), CM (21.9)</td>
</tr>
<tr>
<td>11</td>
<td>41</td>
<td>F</td>
<td>Stable</td>
<td>RCA</td>
<td>CO (26.3), CO (52.3), EC (27.7)</td>
</tr>
<tr>
<td>12</td>
<td>49</td>
<td>M</td>
<td>Variant</td>
<td>LAD</td>
<td>CO (25.5)</td>
</tr>
<tr>
<td>13</td>
<td>67</td>
<td>M</td>
<td>Variant</td>
<td>LAD</td>
<td>CO (36.1), CM (67.1)</td>
</tr>
<tr>
<td>14</td>
<td>53</td>
<td>M</td>
<td>Variant</td>
<td>LCx</td>
<td>CO (29.0)</td>
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<tr>
<td>15</td>
<td>46</td>
<td>F</td>
<td>Variant</td>
<td>RCA</td>
<td>EC (20.0), CM (31.3)</td>
</tr>
</tbody>
</table>

LCx, left circumflex coronary artery; RCA, right coronary artery; LAD, left anterior descending coronary artery; CO, concentric; EC, eccentric; CM, complicated. Coronary stenosis severity (% lumen diameter reduction) in parentheses.

depression) at between 5 and 7 METS. Four patients (3 men, 1 woman) 46 to 67 years old (mean, 53.8±8 years) had variant angina with a history of spontaneous, predominantly early-morning attacks, a negative exercise test result, but positive ergonovine test result with ≥0.1 mV ST segment change. The coronary arteriographic findings are listed in Table 1. Patients were excluded from the study if they had diabetes mellitus, recent myocardial infarction, left ventricular hypertrophy (on echocardiography), left ventricular dysfunction (left ventricular ejection fraction <50%), or valvular heart disease.

Serotonin creatinine sulfate was prepared for human use by the Hammersmith Hospital Pharmacy and stored at −20°C in ampules containing 5 mL of 10⁻² mol/L solution until just before use. The stock solution was diluted with normal (0.9%) saline to achieve final infused concentrations of 10⁻⁴ through 10⁻¹ mol/L.

Invasive Protocol

Two ECG leads were monitored continuously throughout the study. Femoral arterial pressure, heart rate, and two ECG leads were recorded during the last 30 seconds of each infusion period. After the diagnostic study, an optimal radiographic projection was chosen to visualize the coronary artery to be studied, and the position of the image intensifier was subsequently kept constant. Heparin was not routinely administered. The artery studied was chosen to comply with the Research Ethics Committee’s requirements that severe stenoses (>80% reduction in diameter) be avoided. Ten left and five right coronary arteries were studied. In four patients, the infused artery supplied collaterals to an occluded vessel. In the patients with variant angina, the infused artery was that corresponding to the ischemic territory on ergonovine testing assessed by the ECG changes.

All infusions were administered through 8F Judkins catheters at room temperature at a rate of 1 mL/min with a syringe pump (Perfusor, Braun-Melsungen). We have previously shown that random fluctuations in coronary luminal diameter or systematic changes caused by repeated infusions of saline or injections of contrast medium are insignificant.¹⁴ The patients therefore received a single 2-minute infusion of vehicle solution (0.9% saline) followed by 2-minute infusions of serotonin of increasing concentrations from 10⁻⁷ to 10⁻⁴ mol/L followed by an intracoronary bolus dose of isosorbide dinitrate (2 mg in 2 mL of saline) (Fig 1). Angiography was performed with a hand injection of 6 to 8 mL nonionic contrast at baseline, after each infusion, and after isosorbide dinitrate (Fig 1). Before each angiogram, the catheter was emptied to avoid the effects of bolus administration of serotonin.

Tachyphylaxis to the effects of serotonin is frequently observed in animal models. Therefore, in 4 patients with chronic stable angina, we initially compared the coronary diameter change induced by repeated infusion of the same concentration of serotonin after an initial infusion of saline. An arteriogram was performed at baseline, after the infusion of saline, and immediately...
after the initial infusion of serotonin (mean coronary artery diameter at baseline, 2.50±0.36, after saline 2.53±0.35, and after serotonin 1.89±0.34 mm). Another arteriogram was performed 5 minutes later (mean coronary artery diameter at the second baseline, 2.52±0.36 mm). The infusion of serotonin was then repeated and another arteriogram was performed (mean coronary artery diameter after repeat serotonin, 1.88±0.34 mm; P=NS compared with initial infusion). Finally, an intracoronary bolus dose of isosorbide dinitrate (2 mg in 2 mL of saline) was administered, and an arteriogram was performed 2 minutes later (mean coronary artery diameter after nitrate, 2.7±0.37 mm).

**Quantitative Coronary Angiography**

The arterial segments in each frame were analyzed in random order by quantitative computerized analysis with an automated edge contour detection analysis system (Computerized Angiographic Analysis System [CAAS], Version 2V2; Pie Data Medical). End-diastolic frames from each arteriogram were selected for analysis. The angiographic catheter was used as a scaling device, and this, together with the pincushion-distortion correction, allowed the diameters to be recorded as absolute values (expressed in millimeters). All major coronary arteries were divided into thirds according to the American Heart Association classification, and for the purpose of the study, angiographically normal segments located in the proximal and distal thirds (removed from all stenoses) were analyzed. Recorded variables at baseline and after saline, serotonin, and nitrate administration were (1) the diameter of angiographically normal proximal and distal segments; (2) the location of stenoses, defined as the site of minimal lumen diameter relative to side branch origins (Table 1); (3) the minimum diameter of stenoses in millimeters; (4) minimum luminal diameter in millimeters of the reference segment just proximal to the stenosis (Fig 2); and (5) qualitative and quantitative classification of stenosis morphology. Stenoses were morphologically classified as concentric, eccentric, or complicated by two blinded independent observers on the basis of visual inspection of arteriograms recorded in two orthogonal projections. This classification of stenosis was compared with that obtained by computerized symmetry analysis (CAAS symmetry index) of the same coronary lesions. Concentric stenoses were defined as those producing symmetric narrowing, with smooth borders or only very mild irregularity (symmetry index >0.5 to 1) that looked similar in orthogonal projections. Eccentric stenoses were defined as asymmetric narrowing with smooth borders and a broad neck (symmetry index, 0.0 to ≤0.5). Complicated stenoses were defined as asymmetric narrowings with irregular borders and/or overhanging edges (type II of Ambrose et al) or with an “abrupt proximal face” or a “rough” or “sawtooth” component.

Ninety-eight percent of stenoses were classified in the same way by both observers. Quantitative analysis of coronary arteriograms was carried out by two independent observers, who blindly reanalyzed the films at a remote time for reproducibility of the method. No significant intraobserver or interobserver variability was found (ANOVA F=0.3, P=.75). The findings of computer symmetry analysis and qualitative assessment were concordant in 35 stenoses (94%) and discordant for 3 stenoses (2 irregular, 1 eccentric), and these were classified by consensus. All the measured diameters were within 0.07 mm of the mean value of those obtained from computerized measurement by the two independent operators. In a separate study, we analyzed the intraobserver and interobserver variability of the CAAS system in our institution. Twenty-four arterial segments were analyzed by two independent observers and reanalyzed at a remote time. The mean intraobserver variation, expressed as the standard error of the estimate (SEE), was 0.12 mm. The interobserver variation (SEE) was 0.10 mm.

**Statistical Analysis**

All data are expressed as mean±SEM. For comparisons of hemodynamic data and coronary artery diameters (in millimeters), a one-way ANOVA with an allowance for repeated measures was performed. When an F value was found to be significant, a two-tailed Student's t test for paired observations with the Bonferroni correction was used to test differences among means. A value of P<.05 was considered significant.

**Results**

**Stenosis Morphology**

Thirty-eight of the 47 coronary stenoses (14 concentric, 11 eccentric, and 13 complicated) observed in these 15 patients (9 in patients with variant angina: 3 concentric, 3 eccentric, and 3 complicated) were suitable for quantitative analysis, and the results below refer to these stenoses. The severity of coronary stenoses for the whole group ranged from 20% to 77% (mean, 36.2±2.3%) luminal diameter reduction (9 stenoses ≥50%: 4 complicated, 2 eccentric, 3 concentric) (Table 1). The mean percent minimum luminal diameter at baseline was not significantly different in concentric, eccentric, and complicated stenoses (36.0±2.9%, 31.8±3%, and 40.1±5.4%, respectively). Complicated stenoses were longer than concentric and eccentric (6.8±0.95 versus 3.06±0.22 versus 2.78±0.49 mm, respectively; P<.05).
Response of Concentric, Eccentric, and Complicated Stenoses to Serotonin

Mean aortic pressure and heart rate remained unchanged during intracoronary administration of serotonin up to and including the onset of myocardial ischemia, which occurred in all patients as evidenced by angina and/or ST segment change. A change in the ST segment occurred in seven patients with chronic stable angina (depression in four, elevation in three) and in all patients with variant angina (elevation in three and depression in one). In all patients, myocardial ischemia was promptly relieved by intracoronary administration of isosorbide dinitrate. Three patients (two with variant angina, one with stable angina) developed coronary artery occlusion at the site of an irregular lesion, promptly relieved by intracoronary isosorbide dinitrate. During the highest tolerated dose of serotonin, 5 of 13 reference segments (38%) proximal to complicated ste-

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Baseline</th>
<th>Serotonin</th>
<th>Nitrates</th>
<th>Baseline</th>
<th>Serotonin</th>
<th>Nitrates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum Luminal Diameter, mm</td>
<td></td>
<td></td>
<td>Minimum Luminal Diameter, mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentric (n=14)</td>
<td>2.99±0.11</td>
<td>2.64±0.12</td>
<td>3.20±0.12</td>
<td>1.26±0.09</td>
<td>1.01±0.11</td>
<td>1.51±0.11</td>
</tr>
<tr>
<td>Eccentric (n=11)</td>
<td>2.89±0.17</td>
<td>2.49±0.14</td>
<td>3.13±0.20</td>
<td>1.41±0.14</td>
<td>0.95±0.02</td>
<td>1.68±0.19</td>
</tr>
<tr>
<td>Complicated (n=13)</td>
<td>3.24±0.14</td>
<td>2.62±0.15</td>
<td>3.44±0.17</td>
<td>1.42±0.10</td>
<td>0.97±0.08</td>
<td>1.66±0.15</td>
</tr>
</tbody>
</table>

No significant difference between groups (P=NS) after serotonin and nitrates. Percentage change from baseline in parentheses. Figures given are for stable and variant angina patients combined.
noses, 5 of 14 reference segments (36%) proximal to concentric stenoses, and 6 of 11 reference segments (54%) proximal to eccentric stenoses reduced their luminal diameter by >10% ($P=NS$). The magnitude of coronary constriction was similar in the angiographically normal segment proximal to concentric, eccentric, and complicated stenoses (Table 2). The magnitude of coronary constriction distal to the stenoses was also similar in the angiographically normal segment distal to concentric, eccentric, and complicated stenoses (Table 2). During the infusion of the maximum concentration of serotonin, a significantly larger proportion of complicated stenoses than concentric stenoses constricted by ≥20% (100% versus 50%, respectively; $P<.05$; Table 3), and the magnitude of vasoconstriction was greater in complicated than concentric and eccentric stenoses and greater in eccentric than concentric stenoses ($P<.05$) (Table 4, Fig 3). For complicated stenoses, the magnitude of constriction (diameter at baseline minus diameter after serotonin) was greater than that of the reference segments (0.85±0.16 versus 0.42±0.12 mm, respectively; $P<.05$), whereas it was similar to that of reference segments for concentric (0.25±0.05 versus 0.27±0.06 mm, respectively; $P=NS$) and eccentric (0.57±0.13 versus 0.39±0.14 mm, respectively; $P=NS$) stenoses (Fig 4). The severity of the 38 stenoses at baseline did not correlate with the magnitude of vasoconstriction induced by serotonin irrespective of the type of morphology (Fig 5), whereas there was a weak correlation ($r=.39$, $P<.05$) between the length of stenoses and the magnitude of vasoconstriction (Fig 6).

**Stenosis Morphology and Response to Isosorbide Dinitrate**

Intracoronary isosorbide dinitrate had no significant effect on mean aortic pressure or heart rate. There was no difference in its effect on proximal or distal reference segments of concentric, eccentric, and complicated stenoses (Table 2). It increased the coronary luminal diameter of eccentric stenoses more than that of concentric ($P<.05$) and that of complicated ($P<.05$) stenoses (Table 4, Fig 3). A larger proportion of eccentric than of either concentric or complicated stenoses showed dynamic behavior (≥20% increase from baseline) (Table 3).

**Relation Between Stenosis Morphology, Stenosis Reactivity, and Clinical Syndrome**

The prevalence of smooth lesions (concentric and eccentric) and irregular lesions was not significantly

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**Table 3. Proportion of Stenoses With Dynamic Reactivity (≥20% Change From Baseline) In Response to Intracoronary Serotonin and Nitrates in Patients With Angina**

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Stable Angina</th>
<th>Variant Angina</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentric (n=14)</td>
<td>5/11</td>
<td>2/3</td>
<td>7/14</td>
</tr>
<tr>
<td>Eccentric (n=11)</td>
<td>5/8</td>
<td>3/3</td>
<td>8/11</td>
</tr>
<tr>
<td>Complicated (n=13)</td>
<td>10/10</td>
<td>3/3</td>
<td>13/13*</td>
</tr>
</tbody>
</table>

In each column, the first number gives the reactive stenoses and the second number gives the analyzed stenoses.

*P<.05 compared with concentric stenoses.

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**Table 4. Reactivity of Concentric, Eccentric, and Complicated Stenoses to Intracoronary Serotonin and Nitrates**

<table>
<thead>
<tr>
<th>Morphology</th>
<th>No.</th>
<th>Baseline</th>
<th>Serotonin</th>
<th>Nitrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentric Stable angina</td>
<td>11</td>
<td>1.48±0.15</td>
<td>1.23±0.12 (−15.7±2.6)</td>
<td>1.65±0.15 (+13.6±3.6)</td>
</tr>
<tr>
<td>Variant angina</td>
<td>3</td>
<td>1.65±0.35</td>
<td>1.38±0.28 (−15.5±8.1)</td>
<td>1.78±0.30 (+6.5±3.4)</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>1.52±0.14</td>
<td>1.26±0.11 (−15.68±2.8)</td>
<td>1.68±0.13 (+12.05±3.1)</td>
</tr>
<tr>
<td>Eccentric Stable angina</td>
<td>8</td>
<td>1.79±0.14</td>
<td>1.21±0.17 (−31.8±3)*</td>
<td>2.12±0.18 (+20.2±4)*</td>
</tr>
<tr>
<td>Variant angina</td>
<td>3</td>
<td>1.27±0.28</td>
<td>0.73±0.20 (−40.8±10)</td>
<td>1.46±0.40 (+15.6±2.1)</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>1.65±0.15</td>
<td>1.08±0.14 (−32.08±4.1)*</td>
<td>1.94±0.21 (+19.21±3.1)*</td>
</tr>
<tr>
<td>Complicated Stable angina</td>
<td>10</td>
<td>1.51±0.23</td>
<td>0.79±0.16 (−51.8±7.3)†</td>
<td>1.66±0.20 (+11.2±2.9)</td>
</tr>
<tr>
<td>Variant angina</td>
<td>3</td>
<td>1.50±0.30</td>
<td>0.24±0.23 (−77.3±17)</td>
<td>1.71±0.35 (+10.5±4.1)</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>1.51±0.19</td>
<td>0.66±0.14 (−57.69±7.6)‡</td>
<td>1.67±0.13 (+11.04±2.6)</td>
</tr>
</tbody>
</table>

Percentage change from baseline in parentheses.

*P<.05 compared with concentric stenoses.

†P<.001 compared with concentric stenoses.

‡P<.001 compared with concentric and $P<.05$ compared with eccentric stenoses.
different in patients with chronic stable angina and in patients with variant angina. In patients with variant angina, 2 of 3 concentric, all eccentric, and all complicated stenoses showed a ≥20% change of the baseline caliber in response to serotonin, whereas in patients with stable angina, 5 of 11 concentric (45%), 5 of 8 eccentric (62.5%), and all complicated stenoses showed a ≥20% change in response to serotonin (*P < .05 compared with concentric stenoses) (Table 3). There was greater reduction in luminal diameter at the site of complicated stenoses in response to serotonin in variant angina patients compared with stable angina patients (from 1.50 ± 0.30 to 0.24 ± 0.2 mm versus 1.51 ± 0.23 to 0.79 ± 0.16 mm), but the difference did not achieve statistical significance at the site of concentric and eccentric stenoses.

**Fig 3.** Graphs showing luminal diameter changes in concentric (left panels), eccentric (middle panels), and complicated (right panels) stenoses in patients with stable angina (group A) and in patients with variant angina (group B). Responses in individual patients to the maximum concentration of intracoronary infusion of serotonin and intracoronary injection of isosorbide dinitrate (nitrate) are expressed as a change in absolute diameter (in millimeters) and as a percentage of the baseline diameter.

**Fig 4.** Bar graph showing magnitude of stenosis and of reference segment constriction expressed as diameter at baseline minus diameter after serotonin, for concentric, eccentric, and complicated stenoses. Complicated stenoses showed significantly greater constriction than the reference segments.

**Fig 5.** Scatterplot showing correlation between stenosis severity (percentage from baseline reference segment) and the magnitude of vasoconstriction induced by serotonin expressed as percent change in coronary artery diameter from that in the control condition. Linear regression analysis did not show a significant correlation between these two variables.
Irregular (complicated) stenoses showed a significantly greater reduction in caliber after intracoronary serotonin than smooth lesions (concentric and eccentric) both in patients with stable angina (51.8±7.3% versus 22.5±4.1%) and in patients with variant angina (77.3±17% versus 28.2±8.1%) (Fig 7). The stenosis reactivity was independent of eccentricity ratio both in stable angina and in variant angina. In stable angina, 16 stenoses with a concentric ratio and 13 stenoses with an eccentric ratio developed similar caliber reduction in response to serotonin (29.07±6.5% versus 36.96±5.8%, P=NS). Furthermore, in variant angina, 4 stenoses with a concentric ratio and 5 stenoses with an eccentric ratio developed similar caliber reduction in response to serotonin (36.7±18% versus 50.8±14%, P=NS).

Discussion

The results of this study show that complicated coronary stenoses are more likely to constrict significantly and to a greater degree in response to serotonin than eccentric and concentric stenoses in both patients with chronic stable angina and those with variant angina. Furthermore, the enhanced constriction is focal at the site of the stenosis, as indicated by the results showing a larger change in luminal diameter at the site of the stenosis than at the adjacent reference arterial segment. The degree of enhanced constriction is only weakly related to stenosis length and is unrelated to baseline minimum luminal diameter. Eccentric (smooth) stenoses constrict more than concentric (smooth) but less than complicated (irregular) stenoses.

Coronary Effects of Serotonin

Serotonin binds to 5-HT\(_2\) receptors on endothelial cells to stimulate the release of relaxing factor\(^{23}\) and to 5-HT\(_2\) receptors on smooth muscle cells, stimulating their contraction. When the vascular endothelium is normal, the relaxing factor predominates, leading to vasodilatation.\(^{14}\) But if the endothelium is absent, injured, or dysfunctional, as may occur in atherosclerosis, the 5-HT\(_2\) receptor effect predominates, leading to vasoconstriction.\(^{15,25,26}\) Only constriction was seen in those with arteriographic evidence of coronary disease; it was focal and extreme in the patients with variant angina.\(^{14}\)

Serotonin, Platelets, and Coronary Disease

Studies of the response of isolated dog\(^9,26\) and pig\(^8,13,27\) coronary arteries to aggregating platelets show endothelium-dependent relaxation. Fols et al\(^28\) have shown that a severe stenosis in a coronary artery leads to local platelet adhesion and aggregation with phasic reductions in flow through the vessel consistent with either embolization, coronary constriction, or a combination of both events. Sampling of coronary venous blood in patients with coronary atherosclerosis and unstable angina shows elevated plasma levels of serotonin,\(^29\) presumably caused by platelet activation in the vascular bed supplied by the diseased artery or at the site of atheromatous lesions in the diseased artery. These elevated levels would appear to be sufficient to cause constriction of the diseased artery. Although a severe stenosis may induce platelet aggregation, it is not necessary for platelet adhesion, and our study shows that the magnitude of the constrictor effect of serotonin is related not to stenosis severity but to stenosis morphology.

Stenosis Severity, Morphology, and Response to Serotonin

Apart from severe stenosis, there are other mechanisms by which an atheromatous plaque can activate platelets. Exposure of intima to blood will lead to platelet adhesion, activation, and possibly aggregation. This may occur by a deficiency of endothelial covering of the diseased intima or by rupture of an atheromatous plaque. Activation of the coagulation mechanism is, in itself, a stimulus to platelet activation by the formation of thrombin. It is possible that intracoronary serotonin levels were higher in our patients with complex stenosis because of a greater amount of platelet activation than in the other patients, and therefore, higher local serotonin levels may have been present during serotonin infusion. However, there was no indication that baseline local serotonin levels were sufficiently high to increase resting vasomotor tone, since the dilator effect of isosorbide dinitrate was no greater at complex stenoses than at simple concentric stenoses.

Eccentric stenoses showed enhanced vasoconstriction compared with concentric stenoses. This probably re-
fects the presence of an arc of normal muscle able to react to vasoconstrictor stimuli, whereas concentric stenoses tend to be “fixed” by the involvement of the whole circumference of the artery in the atherosclerotic process. Less smooth muscle is available in concentric stenoses to respond to vasoactive stimuli. In an experimental animal model, Ichikawa et al. described the effects of serotonin on coronary blood flow in the presence of coronary stenosis and demonstrated that the effects differed depending on whether the stenosis was compliant or fixed. The authors suggested that this effect is mediated by non-S2-serotonergic receptors.

The eccentric nature of the stenosis with an arc of normal media is unlikely to be the explanation for the observed response in complicated stenoses, since these, like concentric stenoses, tend not to be pliable, as indicated by their poor dilator response to nitrates. The greater length of complicated stenoses could be partly responsible, since the more extensive endothelial involvement by disease may expose a greater total number of smooth muscle cells to 5-HT-induced contraction unopposed by local endothelium-derived relaxing factor production. Local myogenic propagation of the constrictor response could lead to its amplification, with greater reduction of luminal diameter. However, the correlation of the enhanced constrictor response with stenosis length is weak.

Possible explanations of the enhanced constrictor response include greater density of 5-HT smooth muscle constrictor receptors because of upregulation, more profound local reduction in dilator receptor activity, and an exaggerated contractile response of smooth muscle cells at that site to 5-HT receptor stimulation. Further studies are required to investigate the actual mechanism involved. However, irregular morphology of the stenosis does appear to be a marker of this enhanced response and therefore of the underlying mechanism.

Relation of Coronary Stenosis Morphology to Clinical Presentation

Complex coronary stenosis morphology is a common finding in patients with unstable angina and myocardial infarction. It appears to be caused by a ruptured plaque alone or together with a nonocclusive thrombus. It may also be caused by a recanalized thrombus. It is unknown whether the development of complex plaque morphology in these patients occurs before the onset of the acute coronary syndrome or coincides with its onset. The incidence of complex stenosis morphology in patients with unstable angina is about 60%–33% in patients with chronic stable angina, it is about 20% to 30%, and these findings are in agreement with those of our study population with stable angina.

In a large proportion of patients with acute coronary syndromes, evidence of enhanced vasoconstriction at the site of stenosis has been reported and could be explained by the effect of locally released serotonin on vascular smooth muscle receptors in the presence of diseased endothelium.

Clinical Implications

The presence of eccentric or complicated atheromatous plaques even without severe luminal stenosis could, by enhanced vasoconstriction at the site of the plaque caused by changes in functional receptor density, particularly of 5-HT1 and 5-HT2 subtypes, explain the variation in effort tolerance seen in some patients with chronic stable angina and also the attacks of angina at rest seen in patients with unstable angina. The detection of such plaques may therefore provide prognostic information and also assist in identifying patients likely to benefit from coronary vasodilator drugs (Fig 2). Furthermore, specific constrictor receptor blocking agents might be expected to have a greater beneficial effect in patients with such lesions. They could prevent the progression of such complicated plaques to occlusion in acute myocardial infarction and unstable angina, in which preexisting lesions may not be associated with severe stenoses.

More detailed in vivo studies of plaque morphology and tissue characterization are required using newer techniques such as angioscopy and coronary ultrasound imaging to further elucidate their relation to the density of receptors mediating coronary vasoconstrictor responses.

Conclusions

In patients with chronic stable angina and with variant angina, the magnitude of the vasoconstrictor response to serotonin at the site of an atheromatous coronary plaque depends on the morphological characteristics of the plaque, particularly irregularity, and is independent of stenosis severity. This relation suggests that variations in receptor type and density or in the smooth muscle cell response to stimulation may determine the clinical manifestations of coronary disease.

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Circulation. 1993;88:1518-1526
doi: 10.1161/01.CIR.88.4.1518
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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