Vasoreactivity of the Culprit Lesion in Unstable Angina

Peter Bogaty, MD; David Hackett, MD; Graham Davies, MD; Attilio Maseri, MD

Background Although abnormal vasoconstriction may be involved in the pathogenesis of the acute coronary syndromes, the vasoreactivity of the lesion responsible for unstable angina (culprit lesion) has not been directly investigated. It is also unknown if enhanced vasoreactivity is found downstream to this lesion or extends to uninvolved coronary arteries.

Methods and Results We studied seven unstable angina patients whose condition had sufficiently stabilized to allow ergometric bicycle exercise and a cold pressor test to be performed as provocative stimuli during coronary arteriography. We measured the luminal diameter of the culprit lesion, a normal-appearing distal segment, and the segment of an uninvolved coronary artery using quantitative coronary angiography. Seven stable angina patients served as controls. Antianginal medications were tapered and interrupted. The culprit lesion constricted significantly with exercise and the cold pressor test compared with a stable angina control lesion. The culprit lesion measured 1.41±0.07 mm at baseline and diminished to 1.09±0.07 mm with exercise (P=.001). It measured 1.26±0.07 mm before the cold pressor test and diminished to 1.09±0.03 mm with this test (P=.015). In contrast, the profile of the stable lesion in the stable angina control group differed significantly (P=.006). Its luminal diameter measured 1.42±0.17 mm at baseline and 1.48±0.21 mm with exercise (P=NS). It measured 1.57±0.18 mm before and 1.55±0.18 mm with the cold pressor test (P=NS). There were no significant changes to these stimuli in the uninvolved coronary artery segments in unstable angina and in the distal segments in both unstable and stable angina patients.

Conclusions This study demonstrates increased vasoreactivity of the culprit lesion in unstable angina compared with a control lesion in stable angina. The lack of an effect either in the uninvolved coronary artery or downstream to the culprit lesion suggests that systemic neurohumoral or seeding mechanisms are not operative. This abnormal vasoreactivity might predispose to, or be a marker for, the recurrence of acute ischemia at this site.

Key Words • angina  •  vasconstriction  •  arteries

These considerations led to the present study. We evaluated the vasoreactivity of the culprit lesion, a coronary segment distal to the lesion, and a segment of a neighboring coronary artery following unstable angina using ergometric bicycle exercise and the cold pressor test as provocative stimuli during coronary arteriography and compared these findings with those of a group of patients with stable angina.

Methods

Patients

All patients consecutively hospitalized in the Cardiovascular Unit of Hammersmith Hospital with a diagnosis of unstable angina were considered for this study. Excluded were patients with a history of coronary artery bypass surgery or coronary angioplasty; patients with ECG evidence of complete bundle branch block, left ventricular hypertrophy and strain, Wolf-Parkinson-White syndrome, or pacemaker ventricular rhythm; and patients with concomitant cardiomyopathy, significant valvular disease, or a secondary cause for their acute syndrome such as anemia, hyperthyroidism, or an arrhythmia.

Unstable angina was defined as angina appearing at rest or on minimum exertion that was either new-onset angina or a sharp and significant change in the pattern of established angina. Documentation of ST-T changes was required, and serum creatine kinase levels had to remain at least twice the upper normal limit.

Those patients meeting these criteria were eligible for the study only if they had stabilized sufficiently to be able to perform an exercise test and if this test was clinically indicated. The study protocol had been approved by the Research Ethics Committee of Hammersmith Hospital, and written informed consent was required.
Patients stabilizing after 2 to 4 days of usual therapy for unstable angina (always aspirin, often heparin, and usually some combination of β-blockers, nitrates, and calcium antagonists) were considered for the study. After consent was obtained and under continuous ECG monitoring, all antianginal medication was reduced and, if possible, stopped. β-Blockers were stopped at least 24 hours before study. No patient was studied if he or she had received a calcium antagonist or a long-lasting nitrate less than 12 hours before study. Intravenous nitroglycerin was stopped at least 6 hours before study. Patients had to be angina-free for at least 48 hours before exercise testing. If one trial of medication withdrawal had ended in failure, only one other trial was attempted. Aspirin and other drugs were stopped if warranted but, in the case, heparin were continued without modification. No sedative drugs were administered before or during cardiac catheterization.

Patients with typical chronic stable angina and an exercise test positive for ischemia undergoing diagnostic coronary angiography served as a control group after giving written informed consent. Their antianginal medications were stopped 12 to 18 hours before testing.

All studies on all patients were undertaken in midmorning with patients in a fasting state.

Study Protocol

After diagnostic left ventriculography and coronary arteriography using the Judkins technique were performed, the following conditions were necessary to proceed with the study: (1) a stable, angina-free, cooperative patient; (2) absence of a left main stem lesion, an ostial lesion, or severe proximal two- or three-vessel disease; and (3) a clearly identifiable culprit lesion that was not occluded or subtotaly occluded, ie, without incomplete or retarded flow and with a luminal diameter that had contours that could be clearly defined. Identification of the culprit lesion relied on a consideration of anatomic factors (four had only a single coronary lesion), the architecture of the lesion (irregular or complex), the localization of ECG changes, and, in two cases, comparison with a prior angiographic film.

A femoral sheath was then inserted, and a radiotransparent 12-lead ECG was applied. The optimal view for visualizing the culprit lesion was selected, and this view with the same positioning of the image intensifier was maintained throughout the study. The patient's feet were secured on the pedals of a bicycle ergometer. A baseline arteriogram and ECG were taken. The same amount of contrast (Omnipaque 350, Nycomed) and the same rate of injection were subsequently used. The patient was instructed to pedal at a set rate for 90 seconds in increments of 25 W. The angiographer kept the sheath and catheter secure during exercise with periodic fluoroscopy to verify catheter position. Arterial pressure, cardiac rhythm, and the ECG were continuously monitored, and a 12-lead ECG was taken at each stage. End points for terminating exercise were the same as those during standard exercise testing in these patients: limiting symptoms, a heart rate ≥120/min, ST-segment depression of ≥2 mm, and a drop in blood pressure or an arrhythmia. Immediately on terminating exercise, an arteriogram was taken. The bicycle was removed, and the patient rested for 15 minutes. After another baseline arteriogram and ECG, a cold pressor test was administered. The patient placed a hand and forearm in a basin containing a slurry of ice water for 90 seconds, and an arteriogram and ECG were taken at 80 seconds. Intracoronary isosorbide dinitrate (2 mg in 2 mL of saline) was then infused, and a final arteriogram and ECG were taken.

The luminal diameter of the culprit lesion and of a normal-appearing segment of the same artery downstream, but not immediately adjacent to this lesion, were measured. When the culprit lesion was in the territory of the left anterior descending or circumflex coronary artery, a segment of the uninvolved artery, if possible a diseased or irregular segment, was also measured to evaluate the presence of a possible systemic neorohumoral mechanism in unstable angina. In the stable controls, a stenosis was measured as well as a normal-appearing segment distal to this stenosis.

Quantitative Coronary Angiography

Coronary angiograms were analyzed using a contour detection computer analysis system (COMPUTERISED ANGIOGRAPHIC ANALYSIS SYSTEM [CAAS], Pie Data Medical). The size of the stem of the Judkins coronary catheter was used for calibration in millimeters, and correction was made for radiographic pincushion distortion. End-diastolic cine frames were selected and then measured in random order by an experienced technician who was unaware of the study protocol. Identifiable branching points were used for localizing the normal-appearing distal segments selected for analysis. Thirty randomly selected measurements were reanalyzed by a blinded observer. Results were reproducible. The mean of the difference between measurements was 0.07±0.11 mm (P=.6).

Statistical Analysis

Results are expressed as mean±SEM. The two-tailed unpaired t test was used to evaluate differences between the unstable and stable angina groups; within each group, the two-tailed paired t test was used to analyze differences in luminal diameter after an intervention, and this test was also used to evaluate the reproducibility of measurements. Comparison of the pattern of change in luminal diameter between the two patient groups was made using a profile analysis with Hotelling's T2 procedure. A value of P<0.05 was considered significant.

Results

Patient Selection

During the study period of 18 months, 42 consecutive patients presented with unstable angina and characteristic ECG repolarization changes and were hospitalized in the coronary care unit. Seven patients were eligible for and underwent the study and could be analyzed. Of the remaining 35, 7 had prior bypass surgery or coronary angioplasty; 6 were not candidates for exercise testing because of age, poor general medical condition, or cardiac failure, and 2 had a secondary cause for unstable angina; 4 were too unstable to be considered, 1 refused to participate, and 3 did not tolerate medication withdrawal; 3 could not be studied after diagnostic angiography, 1 because the culprit lesion was in the left main stem, 1 because a plaque in the left main stem precluded leaving a catheter in the left coronary ostium during exercise, and 1 because the culprit lesion was in the right coronary ostium. Of the 9 others, 5 had subtotally occluded or occluded culprit lesions precluding measurement, 3 could not be studied because of uncertainty as to the culprit lesion, and the remaining patient had a technically inadequate study. There were no complications in any patient as a result of the study protocol.

Clinical Characteristics: Unstable Angina

Of the 7 patients, 5 were men. The mean age was 56±4 years (range, 36 to 66 years). Four had sustained a prior (>1 month) myocardial infarction. Two of the infarctions were Q wave and two were non-Q wave. One Q-wave infarction and one non-Q-wave infarction were in the territory of the unstable angina culprit artery. Three patients had previously stable angina. Four had one-vessel, 2 had two-vessel, and 1 had three-vessel disease. The left anterior descending coronary artery was studied.
in 4, the circumflex artery in 2, and the right coronary artery in 1. The morphology of the lesion was irregular in 3, eccentric in 3, and concentric in 1. The last episode of chest pain occurred 3.4±0.2 days (range, 2.8 to 4.5 days) before cardiac catheterization.

During the exercise test, 5 patients had ischemic ECG changes, and 4 of these experienced chest pain. During the cold pressor test, 2 had ischemic ECG changes, and 1 of these had chest pain. The work load achieved was 57±11 W (range, 25 to 100 W). Heart rate was 72±2 beats per minute (range, 65 to 80) at rest, 96±6 beats per minute (range, 70 to 114) at peak exercise, 81±4 beats per minute (range, 66 to 95) during the cold pressor test, and 79±2 beats per minute (range, 75 to 83) after nitrates. Resting systolic blood pressure was 155±12 mm Hg (range, 110 to 195); peak exercise systolic blood pressure was 167±12 mm Hg (range, 125 to 210); it was 166±10 mm Hg (range, 120 to 200) during the cold pressor test and 154±9 mm Hg (range, 130 to 170) after nitrates.

**Stable Angina Controls**

These 7 subjects were men aged 53±3 years (range, 39 to 65 years). Five had had a previous infarction. Three had one-vessel, 2 had two-vessel, and 2 had three-vessel disease. The left anterior descending coronary artery was studied in 3, the circumflex artery in 3, and the right coronary artery in 1. Lesion morphology was eccentric in 2, eccentric in 4, and irregular in 1. During exercise, 6 control subjects had ischemic ECG changes, and 5 of these had angina. The cold pressor test was positive for angina and ECG changes in 1 patient. Exercise work load achieved was 89±9 W (range, 50 to 125). Resting heart rate was 63±3 beats per minute (range, 50 to 73) and increasing to 96±5 beats per minute (range, 79 to 120) at peak exercise, 71±4 beats per minute (range, 60 to 84) during the cold pressor test, and 73±4 beats per minute (range, 63 to 88) after nitrates. Resting systolic blood pressure was 151±10 mm Hg (range, 130 to 190); it rose to 171±8 mm Hg (range, 145 to 200) at peak exercise, 176±10 mm Hg (range, 150 to 220) during the cold pressor test, and 133±5 mm Hg (range, 115 to 150) after nitrates.

The only significant differences between the unstable and stable angina patients with regard to these parameters were the lower resting heart rate and the greater work load achieved in the stable angina group (P=.04 for both).

Four unstable patients and 3 stable patients were current smokers. No patient smoked from hospital admission to study. The responses of the arteries to provocative stimuli were similar in smokers and non-smokers within the unstable and stable groups.

**Angiographic Results: Culprit Lesion**

The luminal diameter of the unstable culprit lesion measured 1.41±0.07 mm at baseline; it diminished to 1.09±0.07 mm with exercise (P=.001). It measured 1.26±0.07 mm before the cold pressor test and diminished to 1.09±0.03 mm with this test (P=.015). The lesion then dilated to 1.37±0.04 mm with nitrates (P=.001) (Fig 1). The luminal diameters of the culprit lesion and of the stable angina control lesion for each of the patients with each of the interventions appear in Table 1. The direction of change with exercise was consistent for all 7 unstable angina patients and almost similarly consistent but of a lesser order of magnitude with the cold pressor test.

**Stable Angina Control Lesion**

The profile of the stable lesion in the control group differed significantly (P=.006) (Fig 1). Its luminal diameter measured 1.42±0.17 mm at baseline and 1.48±0.21 mm with exercise (P=NS). Five of the stable lesions did not change and two dilated with exercise (Table 1). The stable lesion measured 1.57±0.18 mm before and 1.55±0.18 mm with the cold pressor test (P=NS). The response of the stable lesions to the cold pressor test was consistent (Table 1). The stable lesion then dilated to 1.81±0.18 mm after nitrates (P=.02).

The responses of the culprit and control lesions after exercise were quite different. The control lesion at baseline 2, 15 minutes after exercise, had a diameter greater than at baseline 1 (1.57±0.18 mm at baseline 2 versus 1.42±0.17 mm at baseline 1). In contrast, the culprit lesion remained narrower at baseline 2 compared with baseline 1 (1.26±0.07 mm at baseline 2 versus 1.41±0.07 at baseline 1). The difference in diameters of the culprit and control lesions at baseline 2 was significant (P=.04). This comparison is possible because the two lesions were almost identical at baseline 1. Furthermore, although the dilating effect of nitrates after the cold pressor test was of similar magnitude for both lesions (0.28 mm for the culprit lesion versus 0.26 mm for the control lesion), this vasodilation barely allowed the culprit lesion to return to its initial baseline (1.37±0.04 mm with nitrates versus 1.41±0.07 mm at baseline 1), whereas the control lesion dilated considerably in comparison with its diameter at the initial baseline (1.81±0.18 mm with nitrates versus 1.42±0.17 mm at baseline 1, P=.002). These findings are consistent with the presence of increased tonus and a relative resistance to the dilating effect of nitrates at the culprit lesion in unstable angina.

**Unstable Angina Uninvolved Coronary Artery Segments**

In 6 of the unstable patients, the culprit lesion was in the left coronary territory. Therefore, a segment of the uninvolved artery—the left circumflex in 4 patients and the left anterior descending in 2—could also be mea-
TABLE 1. Luminal Diameter of Culprit Lesion and of Stable Angina Control Lesion in Each Patient at Baseline and With Each Intervention

<table>
<thead>
<tr>
<th>Subject</th>
<th>Diameter, mm</th>
<th>Change, %</th>
<th>Diameter, mm</th>
<th>Change, %</th>
<th>Diameter, mm</th>
<th>Change, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 1</td>
<td>Exercise</td>
<td>Baseline 2</td>
<td>CP</td>
<td>NTG</td>
<td></td>
</tr>
<tr>
<td>Unstable angina culprit lesion</td>
<td>1.24 ± 0.04</td>
<td>1.04</td>
<td>1.28 ± 0.03</td>
<td>1.02</td>
<td>1.34 ± 0.06</td>
<td>+3 ± 0.01</td>
</tr>
<tr>
<td>2</td>
<td>1.38 ± 0.08</td>
<td>-22</td>
<td>0.95 ± 0.09</td>
<td>0.99</td>
<td>1.48 ± 0.14</td>
<td>+4 ± 0.09</td>
</tr>
<tr>
<td>3</td>
<td>1.59 ± 0.10</td>
<td>-12</td>
<td>1.20 ± 0.04</td>
<td>1.04</td>
<td>1.22 ± 0.06</td>
<td>+1 ± 0.02</td>
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<tr>
<td>4</td>
<td>1.65 ± 0.03</td>
<td>-38</td>
<td>1.26 ± 0.16</td>
<td>1.16</td>
<td>1.35 ± 0.18</td>
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</tr>
<tr>
<td>5</td>
<td>1.43 ± 0.16</td>
<td>-19</td>
<td>1.22 ± 0.15</td>
<td>1.15</td>
<td>1.50 ± 0.20</td>
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<td>6</td>
<td>1.46 ± 0.10</td>
<td>-25</td>
<td>1.50 ± 1.20</td>
<td>1.20</td>
<td>1.42 ± 0.14</td>
<td>+1 ± 0.02</td>
</tr>
<tr>
<td>7</td>
<td>1.12 ± 0.02</td>
<td>-27</td>
<td>1.40 ± 1.10</td>
<td>1.10</td>
<td>1.25 ± 0.14</td>
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</tr>
<tr>
<td>Mean ± SEM</td>
<td>1.41 ± 0.07</td>
<td>1.09 ± 0.07</td>
<td>-23 ± 3</td>
<td>1.26 ± 0.07</td>
<td>1.09 ± 0.03</td>
<td>-12 ± 4</td>
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<tr>
<td>Stable angina control lesion</td>
<td>1.37 ± 0.04</td>
<td>+25 ± 5</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>2.15 ± 0.09</td>
<td>-3</td>
<td>2.23 ± 0.27</td>
<td>2.27</td>
<td>2.51 ± 0.11</td>
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</tr>
<tr>
<td>2</td>
<td>1.53 ± 0.17</td>
<td>+16</td>
<td>1.86 ± 0.04</td>
<td>2.04</td>
<td>2.08 ± 0.02</td>
<td>+2 ± 0.02</td>
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<td>3</td>
<td>0.92 ± 0.08</td>
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<td>1.17 ± 0.16</td>
<td>1.06</td>
<td>1.13 ± 0.07</td>
<td>+7 ± 0.02</td>
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<tr>
<td>4</td>
<td>1.90 ± 0.22</td>
<td>+19</td>
<td>2.03 ± 1.84</td>
<td>1.84</td>
<td>2.16 ± 0.17</td>
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<td>1.08 ± 0.07</td>
<td>-1</td>
<td>1.05 ± 1.09</td>
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<td>1.76 ± 0.16</td>
<td>+6 ± 0.08</td>
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<tr>
<td>6</td>
<td>1.06 ± 0.10</td>
<td>-6</td>
<td>1.45 ± 1.33</td>
<td>1.33</td>
<td>1.57 ± 0.18</td>
<td>+1 ± 0.02</td>
</tr>
<tr>
<td>7</td>
<td>1.31 ± 0.25</td>
<td>-5</td>
<td>1.21 ± 1.25</td>
<td>1.25</td>
<td>1.46 ± 0.17</td>
<td>+1 ± 0.02</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>1.42 ± 0.17</td>
<td>1.48 ± 0.21</td>
<td>+2 ± 4</td>
<td>1.57 ± 0.18</td>
<td>1.55 ± 0.18</td>
<td>-1 ± 3</td>
</tr>
</tbody>
</table>

CP indicates cold pressor test; NTG, nitrates.

Discussion

We believe this may be the first study that has specifically examined the vasoreactivity of the lesion responsible for unstable angina. The principal findings are: (1) the culprit lesion in unstable angina exhibits a greater vasoconstrictive potential in comparison with a stable coronary artery lesion; (2) a marked vasoconstrictive potential does not appear to extend downstream from the unstable lesion along the distal epicardial vasculature; and (3) a proximal segment of a coronary artery other than the culprit lesion artery appears unaffected by this enhanced vasoreactivity.

The culprit lesion in unstable angina is associated with plaque fissure and superimposed thrombus and aggregated platelets.1-3,8,12 Thrombin is a powerful platelet proaggregant incompletely blocked by heparin26.
TABLE 2. Luminal Diameter of Distal Segment in Each Patient at Baseline and With Each Intervention

<table>
<thead>
<tr>
<th>Subject</th>
<th>Baseline 1</th>
<th>Exercise</th>
<th>Change, %</th>
<th>Baseline 2</th>
<th>CP</th>
<th>Change, %</th>
<th>NTG</th>
<th>Change, %</th>
</tr>
</thead>
<tbody>
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<td>1</td>
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<td>-10</td>
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<td>-4</td>
<td>1.43</td>
<td>+44</td>
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<td>+16</td>
<td>1.12</td>
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<tr>
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<td>0.87</td>
<td>-16</td>
<td>1.05</td>
<td>0.99</td>
<td>-6</td>
<td>0.98</td>
<td>+1</td>
</tr>
</tbody>
</table>

Mean±SEM 1.45±0.17 1.36±0.18 -7±3 1.39±0.18 1.32±0.15 -3±3 1.69±0.24 +26±6

Diameter, mm

Mean±SEM 1.35±0.15 1.41±0.10 +8±6 1.36±0.11 1.26±0.06 -6±3 1.67±0.11 +33±4

CP indicates cold pressor test; NTG, nitrates.

and not inhibited by aspirin27. Thrombin also induces the release of endothelin,28 a powerful vasoconstrictor. Angiographically visible thrombus following coronary angioplasty is associated with focal vasoconstriction.29 Platelets release serotonin and thromboxane A₂. Although production of the latter is inhibited by aspirin,30 the former is not and is vasoconstrictive in the presence of abnormal endothelium.23 In addition, exercise and the cold pressor test, through the increase in shear stress and the rise in catecholamines they provoke, might further potentiate platelet activity.31 Thus, it is not surprising that the pathophysiological substrate of unstable angina manifests an enhanced vasoconstrictive potential.

The unstable angina culprit lesion narrowed by 23% with exercise and by 12% with the cold pressor test; in contrast, the control coronary lesion in stable angina patients did not change significantly with these stimuli. In addition, the difference in the luminal diameters of the unstable lesion and the control lesion at the second baseline several minutes after exercise in comparison to their similar diameters at the first baseline and the relative resistance to nitrates of the unstable lesion compared with the stable control suggest the presence of increased tone at the unstable lesion.

Because there was a trend to vasoconstriction with exercise in the normal-appearing segment distal to the unstable lesion, a seeding effect of chemical mediators released from the unstable lesion, albeit minor, cannot be excluded. Nor can an influence of culprit lesion mediators more distally at the arteriolar level be ruled out.32 Demonstration of such an effect would have required placement of a Doppler catheter past the culprit lesion, a maneuver precluded by the severity of the lesion and the unstable context.

The measurement of a proximal segment of a coronary artery other than the culprit lesion artery permitted consideration of a possible role for a systemic or regional vasoconstrictive effect mediated by a neural or neurohumoral mechanism. No evidence for the presence of such an effect could be shown.

The trend to vasodilation in the normal-appearing segments distal to the stable control lesions did not reach significance. The absence of more pronounced vasodilation in these segments is consistent with the presence of an abnormal endothelium. These patients were likely to have diffuse, even if angiographically inapparent, coronary artery disease because most had multivessel disease, prior infarction, and longstanding angina.

Comparison With Other Studies

Previous studies suggest that the response of a stable atheromatous coronary artery lesion to exercise or to the cold pressor test is either no change33 or vasoconstriction.34-36 A normal segment appears to dilate to these stimuli.34-36 The lack of such a response in diseased arteries may be due to endothelial dysfunction preventing endothelium-derived relaxing factor–mediated vasodilation secondary to increased flow37 and to α₂-adrenergic stimulation,38 both present with exercise and application of cold. Absence of vasodilation could also be due to increased sensitivity of vascular smooth muscle in atheromatous arteries.39 Therefore, the absence of vasodilation in this study in the stable angina control subjects is expected. However, in contrast to three previous studies that documented a reduction in
luminal diameter of 9% to 24% in stable stenotic and irregular coronary lesions to exercise and the cold pressor test,36-38 we were unable to demonstrate vasoconstriction in stable angina control subjects. This was also the case in the study by Matsuda et al.,33 in which 5 of 7 patients with coronary artery disease and ST-segment depression during exercise exhibited no change in their coronary stenoses during exercise. There is probably a certain heterogeneity in the response of diseased arteries to provocation,33,35,36 An arc of pliable vessel wall is required for vasomotion, and this might not be possible in case of a concentric rigid diffusely calcified lesion.40 Moreover, a lingering effect of antianginal medication, particularly calcium antagonists, withdrawn 12 to 18 hours before study cannot be excluded. Small differences in the exact timing from peak exercise to angiography could also account for some of this discrepancy. The vasodilatation to exercise in two stable control lesions (Table 1) was unexpected; such a response to exercise was also noted in one of the diseased segments studied by Gordon et al.36 Inconsistent results in previous studies of vasoactivity with exercise or the cold pressor test might also be caused by heterogeneity of lesions if clinically inapparent relatively unstable lesions exhibited enhanced vasoconstriction, whereas quite stable lesions showed little change or even dilation.

Two previous studies have examined the role of vasoconstriction in acute coronary syndromes. Hackett et al.18 demonstrated vasoconstriction at the culprit lesion in patients with acute myocardial infarction who were undergoing thrombolysis. Bertrand et al.19,20 administered ergonovine in a large consecutive series of patients with various cardiac presentations who were undergoing coronary arteriography. Their study suggested abnormal vasoactivity in myocardial infarction as spasm was provoked in 20% of patients within 1 month of myocardial infarction and in 6.2% of those studied later. However, the degree of narrowing was incompletely characterized, and the relation of spasm to the culprit lesion was not specified. In fact, in 40% of cases, spasm occurred in a non-infarct-related artery. Spasm was also provoked in 38% of a group with resting, mostly nocturnal, angina.41 The most common ECG abnormality in this group was ST-segment elevation during angina, and almost half of the group had normal or nonsignificant coronary artery disease. Thus, the characteristic clinical entity of unstable angina was not specifically described in the study by Bertrand et al.

Study Limitations

The major limitations of this study were imposed by ethical and practical considerations. The number of unstable angina patients was small. Several days had already passed since their initial acute presentation, and they were relatively stabilized at the time of study. By the very nature of the study protocol, they were carefully selected from a much larger cohort in the spectrum of unstable angina and constituted a relatively mild subset of this condition. It would have been impossible to challenge these patients with exercise and the cold pressor test earlier in their presentation of unstable angina. Because their antianginal medication was gradually weaned before study, a persistent effect of these drugs may have presented even greater vasoconstrictive force. A pharmacological challenge like ergonovine or serotonin, precluded because of their unstable condition, might have demonstrated a more powerful effect than that provided by the relatively mild provocative stimuli of exercise or the cold pressor test. Finally, although the accuracy and precision of the quantitative angiographic system used (CAAS) have been validated in the range of lesion diameters measured,42 the possibility of minor error in measurement of arteries close to or less than 1 mm in diameter constitutes a potential limitation of this study. And yet, despite all these limitations, significant, directionally consistent vasoconstriction of the culprit lesion was detected several days after the major manifestations of unstable angina, and this observation was further highlighted by comparison with a stable angina control group.

Conclusions

This study has demonstrated persistent enhanced vasoactivity of the culprit lesion in unstable angina using relatively mild provocative stimuli several days after the most acute manifestations of this condition. This abnormal focal vasoactivity may be due to the continued presence of activated platelets and/or a persistent local procoagulant climate and might predispose to, or be a marker for, the recurrence of acute ischemia at this site. This suggests that the use of specific blockers of vasoconstrictive mediators such as thrombin inhibitors and serotonin receptor antagonists could increase understanding and aid in the management of the unstable lesion.

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