ORIGINAL ARTICLES

Provocation of Coronary Artery Spasm by the Cold Pressor Test

Hemodynamic, Arteriographic and Quantitative Angiographic Observations

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SUMMARY In this study we attempted to determine if the cold pressor test, a known sympathetic reflex-ogenetic stimulus, could precipitate coronary artery spasm. Thirty-five patients undergoing coronary arteriography for evaluation of chest pain syndromes were given the cold pressor test. During 1 minute of cold pressor stimulation, aortic systolic pressure increased 18.1 ± 9.7 mm Hg (mean ± SD) and heart rate did not change significantly. Focal coronary artery spasm was provoked in seven patients, each of whom had an atheromatous plaque at the site of spasm. Four of six patients with a precatheterization clinical diagnosis of variant angina (group 1) had coronary artery spasm, and two of the four had associated ischemic manifestations. Of 14 patients in whom classic angina (group 2) was diagnosed before cardiac catheterization, two manifested focal coronary spasm. One of 15 patients thought to have atypical chest pain (group 3) manifested spasm. There were no significant differences in baseline variables (aortic systolic or diastolic pressure, heart rate, double product and left ventricular end-diastolic pressure) or hemodynamic response (aortic systolic pressure, heart rate or double product) to cold pressor stimulation between patients in each group and between those who manifested spasm and those who did not. Ventricular ectopy and ventricular tachycardia developed in one patient but were readily reversed with intravenous nitroglycerin. Quantitative angiography showed that the luminal diameter of normal coronary segments significantly decreased in each group of patients in response to cold pressor stimulation, but this response was most pronounced in the variant angina group (-12.7 ± 11.5% from control in group 1, -5.1 ± 10.2% in group 2, and -7.9 ± 9.6% in group 3; p < 0.001 for each group). Patients who are prone to coronary spasm may represent one extreme of a spectrum of reactivity to a coronary vasoconstrictive stimulus. The cold pressor test can provoke focal coronary artery spasm in certain patients and may be a useful nonpharmacologic provocative screening test to aid in the diagnosis of this phenomenon.

CORONARY ARTERY SPASM has become the focus of increasing attention. Its role in variant angina is well documented,1-5 and it has been observed in patients with classic angina.6, 7 unstable angina8, 9 and myocardial infarction.10 The transience of coronary artery spasm makes it difficult to diagnose. Consequently, various interventions, primarily pharmacologic, have been used to provoke coronary artery spasm during coronary arteriography. These pharmacologic interventions include the administration of ergot aklaloids,11, 12 epinephrine in combination with propranolol,13 and methacholine.14

The cold pressor test, a sympathetic reflexogenic stimulus, has been shown to increase coronary resistance and reduce coronary blood flow in patients with coronary artery disease, presumably by reflex coronary vasoconstriction.15 The present study was undertaken to determine whether the cold pressor test could precipitate focal coronary spasm and therefore provide a useful, nonpharmacologic provocative test to aid in the diagnosis of this phenomenon. Additionally, the general response of normal and diseased coronary arteries to the cold pressor test was measured using quantitative arteriographic techniques.

Materials and Methods

Thirty-five patients (34 males and one female), mean age of 50.1 years (range 30–62 years), undergoing routine cardiac catheterization and coronary arteriography for evaluation of chest pain syndromes were included in this study. The patients were categorized according to their precatheterization clinical presentation. Group 1 consisted of six patients con-
sidered to have variant angina based on anginal chest pain that usually occurred at rest but might also be provoked by effort and ST-segment elevation, rather than the usual ST depression, during chest pain. Group 2 consisted of 14 patients considered to have classic angina pectoris based on chest pain with effort typical of angina pectoris and ST-segment depression accompanying the chest pain during a treadmill exercise test. Group 3 consisted of 15 patients with atypical chest pain and no definite electrocardiographic manifestations of ischemia.

Cardiac catheterization was performed with the patient in the fasting state after informed consent had been obtained. No routine premedication was administered. Left-heart pressures were measured before arteriography. Selected coronary arteriograms were then obtained in several oblique projections. Next, the cold pressor test was performed by submerging the patient's free hand in ice water for 1 minute while monitoring aortic pressure and two electrocardiographic leads (usually leads I and III). After 1 minute of cold submersion, aortic pressure and heart rate were measured. The catheter was then manipulated to the coronary orifice and an arteriogram was obtained in a selected oblique projection. The patient's hand was removed from the water between coronary injections and, after hemodynamic and electrocardiographic changes returned to baseline (generally 0.5–2 minutes), was resubmerged for the next oblique view. The arteriogram was usually obtained after 1.5–2 minutes of cold submersion. Both coronary arteries were studied during cold pressor stimulation. Nitroglycerin was then administered sublingually and selected additional arteriograms were obtained. Left ventriculography was performed after selective coronary arteriography. Atropine was not used in any of the patients.

In eight patients, an initial dose of 0.5 mg of i.v. ergonovine maleate was administered after the cold pressor test and before nitroglycerin was given. If no chest pain or electrocardiographic changes occurred after 5 minutes, another 0.15 mg i.v. was administered. Two patients received an additional 0.20 mg intravenously. Selected coronary arteriograms were obtained 5 minutes after the last dose of ergonovine or earlier if there were ischemic manifestations. The coronary arteriograms were analyzed by at least two observers. When the two observers did not agree, a third observer was consulted. Coronary artery spasm induced by the cold pressor test was considered to be present if a lesion observed in the control arteriograms progressed to complete (100%) or sub-total (95–99% diameter narrowing) occlusion on cold pressor stimulation or a noncritical lesion became critical (i.e., greater than 50% diameter narrowing) by an increase of at least 25% after cold pressor stimulation. Relief of the spasm by sublingual nitroglycerin was necessary to confirm the finding.

Quantitative coronary arteriography was performed using a Vanguard projector system equipped with a sonic digitizer and Tektronix 31 computer; the system was programmed to measure linear distances. The coronary arteriogram was projected and an end-diastolic frame was selected. The projected luminal diameter of the coronary artery was measured separately by two observers. Measurements were made at a segment of the coronary artery that appeared angiographically normal. Each observer made five measurements at the same location on the vessel, usually at a branch point for reproducibility, and the measurements were averaged. Each coronary artery was measured before and after cold pressor stimulation and after nitroglycerin. Alterations in luminal diameter at the site of stenotic atheromatous lesions were measured in 12 arteries at the point of maximal stenosis. The quantitative angiographic responses to cold pressor stimulation and nitroglycerin were calculated as the percentage of change from control. The height of the image intensifier tower was kept constant during the study and the same oblique projections were used. Hence, changes in measured arterial diameter reflect changes in luminal caliber induced by the intervention.

Statistical comparisons were made using the t test.

**Results**

**Hemodynamic Response**

Hemodynamic measurements for the total group and the three subgroups are shown in table 1. Aortic systolic pressure increased significantly for all groups during cold pressor stimulation, with a mean increase of 18.1 ± 9.7 mm Hg (SD) (p < 0.001). Heart rate did not change significantly from baseline for the total group (3.4 ± 5.1 beats/min, p > 0.05). There were no significant differences between any two groups with regard to baseline aortic systolic and diastolic pressures, heart rate, double product and left ventricular end-diastolic pressure. The only significant intergroup difference in response to the cold pressor test was the change in systolic pressure of group 2 vs group 3 (p < 0.05).

**Arteriographic Response (Focal Spasm)**

The angiographic responses of the three groups of patients to the cold pressor test are shown in table 2. Four of the six patients in group 1 manifested focal coronary artery spasm during the cold pressor test (figs. 1–3). In each case, spasm developed at the site of an atheromatous plaque. Two patients did not develop spasm during the cold pressor test. Two of the 14 patients in group 2 manifested focal coronary artery spasm during the cold pressor test. Patient JW had only a 25% lesion in the right coronary artery despite having classic effort angina and exercise-induced ST-segment depression on treadmill exercise testing. The remaining 12 patients in this group had critical lesions in one or more vessels but none manifested focal spasm during the cold pressor test.

One of the 15 patients in group 3 manifested focal spasm at the site of a minor luminal plaque during cold pressor stimulation. Thirteen of the 14 non-
### Table 1. Hemodynamic Alterations During Cold Pressor Stimulation

<table>
<thead>
<tr>
<th></th>
<th>Total group (n = 35)</th>
<th>Group 1 (n = 6)</th>
<th>Group 2 (n = 14)</th>
<th>Group 3 (n = 15)</th>
<th>Spasm (n = 7)</th>
<th>No spasm (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
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<tr>
<td>Aortic systolic pressure (mm Hg)</td>
<td>128.4 ± 18.8 (95-175)</td>
<td>127.5 ± 21.2 (100-150)</td>
<td>131.5 ± 22.5 (95-175)</td>
<td>124.7 ± 11.1 (105-145)</td>
<td>129.4 ± 19.7 (100-150)</td>
<td>128.2 ± 22.4 (95-175)</td>
</tr>
<tr>
<td>Aortic diastolic pressure (mm Hg)</td>
<td>72.1 ± 8.8 (60-95)</td>
<td>74.9 ± 13.3 (60-95)</td>
<td>69.3 ± 10.9 (60-95)</td>
<td>74.2 ± 6.9 (60-85)</td>
<td>72.8 ± 12.1 (60-80)</td>
<td>71.9 ± 10.2 (60-95)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>68.9 ± 10.8 (50-98)</td>
<td>63.3 ± 9.7 (50-74)</td>
<td>68.2 ± 9.9 (54-83)</td>
<td>73.4 ± 11.7 (62-98)</td>
<td>64.2 ± 9.9 (50-74)</td>
<td>70.1 ± 11.5 (54-98)</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>12.4 ± 4.7 (4-47)</td>
<td>12.0 ± 5.8 (4-20)</td>
<td>13.1 ± 5.5 (6-27)</td>
<td>9.2 ± 2.5 (7-13)</td>
<td>16.2 ± 1.5 (10-20)</td>
<td>11.4 ± 4.8 (4-27)</td>
</tr>
<tr>
<td><strong>Cold pressor</strong></td>
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<tr>
<td>Change in aortic systolic pressure (mm Hg)</td>
<td>18.1 ± 9.7 (5-37)</td>
<td>17.5 ± 10.4 (5-35)</td>
<td>22.3 ± 10.1 (5-37)</td>
<td>12.4 ± 5.9 (5-25)</td>
<td>19.5 ± 12.0 (5-35)</td>
<td>17.8 ± 8.8 (6-37)</td>
</tr>
<tr>
<td>Change in heart rate (beats/min)</td>
<td>3.4 ± 5.1 ((-2)-17)</td>
<td>-1.5 ± 7.0 ((-2)-15)</td>
<td>3.2 ± 3.8 ((-1)-10)</td>
<td>5.2 ± 5.5 (0-17)</td>
<td>2.0 ± 1.7 ((-2)-15)</td>
<td>3.2 ± 5.0 ((-2)-17)</td>
</tr>
<tr>
<td>Change in double product</td>
<td>1730 ± 1117 (190-417)</td>
<td>818 ± 1428 (190-3800)</td>
<td>1958 ± 1021 (320-3974)</td>
<td>1647 ± 1083 (650-4176)</td>
<td>1550 ± 1151 (190-3800)</td>
<td>1715 ± 2108 (320-4176)</td>
</tr>
</tbody>
</table>

Values are mean ± SD (range in parentheses).
Abbreviation: LVEDP = left ventricular end-diastolic pressure.

### Table 2. Arteriographic Response to Cold Pressor Stimulation

<table>
<thead>
<tr>
<th>Pt. (years)</th>
<th>Age</th>
<th>Baseline arteriography</th>
<th>Cold pressor response</th>
<th>Arteriographic</th>
<th>Chest pain</th>
<th>ECG changes</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1 (variant angina)</strong></td>
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<td></td>
</tr>
<tr>
<td>OL</td>
<td>48</td>
<td>LAD 75%; RCA and CFx normal</td>
<td>LAD→complete</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>ES</td>
<td>46</td>
<td>RCA 90%; LCA normal</td>
<td>RCA→subtotal, poor distal flow</td>
<td>No</td>
<td>ST(†)lead III</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>ZB</td>
<td>62</td>
<td>RCA and LCA normal</td>
<td>No focal spasm</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>JT</td>
<td>61</td>
<td>LAD minimal plaque; RCA and CFx normal</td>
<td>LAD→subtotal</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>RH</td>
<td>43</td>
<td>LAD minimal plaque; RCA and CFx normal</td>
<td>No focal spasm</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>ER</td>
<td>49</td>
<td>LAD 70%, CFx 70%, RCA 90%</td>
<td>LAD→complete</td>
<td>Yes</td>
<td>ST(†)leads I and III</td>
<td>Premature ventricular complexes, ventricular tachycardia (responded to i.v. nitroglycerin)</td>
<td>None</td>
</tr>
</tbody>
</table>

**Group 2 (classic angina [positive responders only])**

| Dh            | 61  | LAD 75%; RCA and CFx normal | LAD→subtotal          | No             | None       | None        | None          |
| JW           | 60  | RCA 25%; LCA normal         | RCA→75%               | No             | None       | None        | None          |

**Group 3 (atypical chest pain [positive responder only])**

| Et            | 55  | LCA and RCA minor luminal plaque | LAD→75%, CFx (OM) 50% | No             | None       | None        | None          |

Abbreviations: LAD = left anterior descending coronary artery; RCA = right coronary artery; CFx = circumflex coronary artery; OM = obtuse marginal branch; LCA = left coronary artery.
FIGURE 1. Left coronary arteriograms of patient OL. Left anterior oblique views are shown above, right anterior oblique views are shown below. (A) Baseline arteriogram shows a 75% narrowing of the proximal left anterior descending coronary artery (arrow). (B) During cold pressor stimulation, there was complete occlusion at the site of the lesion. No chest pain or electrocardiographic changes occurred. (C) After sublingual nitroglycerin, the spasm was reversed and distal flow resumed.

FIGURE 2. Coronary arteriograms and electrocardiographic lead III of patient ES. The right coronary artery is shown in the left anterior oblique view. (A) Baseline arteriogram shows 90% stenosis of the middle segment, with good distal runoff. (B) During cold pressor stimulation, the artery was almost totally stenosed at the site of the lesion and only faint flow could be seen beyond the stenosis. Mild ST-segment elevation occurred, although the patient did not experience chest pain. (C) After nitroglycerin, the lesion was less stenosed and distal runoff was good. The ST segments returned to normal.
Two patients with classic angina (group 2) contributed whereas the other patient did not respond to greater narrowing 45 minutes before angina. Another patient with variant angina showed no response to either provocative tests but had been given ergonovine (100% response) or patients with atypical chest pain (group 3) (p = NS). Thirteen of 14 normal arterial segments in group 1 (93%) showed a vasoconstrictor response to cold pressor stimulation, compared with 17 of 26 (65%) in group 2 and 26 of 33 (79%) in group 3.

There was no correlation between the magnitude of coronary artery response and systemic hemodynamic response as measured by the rise in systolic blood pressure (r = 0.123, p > 0.3). The right, left anterior descending and circumflex coronary arteries were equally responsive, with luminal diameter decreasing 8.0 ± 9.3%, 8.4 ± 9.4% and 7.3 ± 12.2% from control, respectively, during the cold pressor test.

Sublingual nitroglycerin produced vasodilatation, with luminal diameter increasing 14.8 ± 15.0% compared with control. The vasodilatation response was not statistically significant for patients in group 1, which might reflect the more pronounced vasoconstriction in these arteries before nitroglycerin administration. In support of this, vasomotor responsiveness, defined as the change in luminal diameter

Figure 3. Left coronary arteriogram and electrocardiographic leads I (upper tracing) and III (lower tracing) of patient ER. (A) The baseline arteriogram shows a 70% lesion in the left anterior descending coronary artery and a 70% lesion in the circumflex artery. (B) During cold pressor stimulation, the left anterior descending coronary artery was completely occluded. The patient had chest pain and ST-segment elevation in leads I and III. The left anterior descending coronary artery in this patient extended around the apex and supplied some of the inferior myocardium.

Comparison of the Cold Pressor Test and Ergonovine Maleate Stimulation

Three patients with variant angina (group 1) received both provocative tests. One patient manifested spasm to both stimuli, but the degree of spasm was more pronounced with ergonovine (100% vs 95%). One patient responded to ergonovine (60% occlusion) but had no focal response to cold pressor. Another patient with variant angina showed no response to either provocative tests but had been given 5 mg of sublingual isosorbide dinitrate for severe chest pain 45 minutes before arteriography, which may have contributed to his failure to respond to provocation. Two patients with classic angina (group 2) underwent both tests. One patient responded to both but with greater narrowing after ergonovine (95% vs 75%), whereas the other patient did not respond to either stimulus. Three patients with atypical chest pain (group 3) showed no focal response to either provocative test.

Quantitative Arteriographic Response

Quantitative measurements were made by two observers. The interobserver correlation tested by linear regression analysis was excellent (r = 0.978, p < 0.001).

The quantitative changes in luminal diameter of normal coronary artery segments and "fixed" atheromatous lesions in response to cold pressor stimulation and nitroglycerin are shown in table 3. During the cold pressor test, a highly significant vasoconstrictor response (i.e., decrease in luminal diameter) was seen in normal segments of arteries in all groups. The magnitude of response, however, was greater in the patients with variant angina (group 1) than in patients with classic angina (group 2) (p < 0.05) or patients with atypical chest pain (group 3) (p = NS). Thirteen of 14 normal arterial segments in group 1 (93%) showed a vasoconstrictor response to cold pressor stimulation, compared with 17 of 26 (65%) in group 2 and 26 of 33 (79%) in group 3.

Sublingual nitroglycerin produced vasodilatation, with luminal diameter increasing 14.8 ± 15.0% compared with control. The vasodilatation response was not statistically significant for patients in group 1, which might reflect the more pronounced vasoconstriction in these arteries before nitroglycerin administration. In support of this, vasomotor responsiveness, defined as the change in luminal diameter
TABLE 3. Quantitative Angiographic Response of Normal
Coronary Segments and Atheromatous Lesions to Cold Pressor
Stimulation and Nitroglycerin

<table>
<thead>
<tr>
<th></th>
<th>% change from control* (mean ± sd)</th>
<th>Range</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal segments</td>
<td></td>
<td></td>
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<tr>
<td>Cold pressor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n = 73)</td>
<td>−7.9 ± 10.3 (−33.8 to 16.3)</td>
<td>&lt; 0.001</td>
<td></td>
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<tr>
<td>Group 1 (n = 14)</td>
<td>−12.7 ± 11.5 (−33.8 to 2.0)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Group 2 (n = 26)</td>
<td>−5.1 ± 10.2 (−22.2 to 13.3)</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Group 3 (n = 33)</td>
<td>−7.9 ± 9.6 (−30.9 to 8.6)</td>
<td>&lt; 0.001</td>
<td></td>
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<tr>
<td>Nitroglycerin</td>
<td></td>
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<tr>
<td>All (n = 70)</td>
<td>14.8 ± 15.0 (−33.3 to 44.8)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Group 1 (n = 11)</td>
<td>6.9 ± 14.8 (−19.5 to 27.2)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Group 2 (n = 26)</td>
<td>13.5 ± 17.7 (−33.3 to 44.8)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Group 3 (n = 33)</td>
<td>18.4 ± 11.7 (−11.1 to 44.2)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Lesions</td>
<td></td>
<td></td>
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<tr>
<td>Cold pressor</td>
<td>−6.5 ± 13.8† (−38.6 to 9.2)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>10.1 ± 19.2† (−7.2 to 60.5)</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

*Data do not include arteries that manifested occlusive focal
spasm.
†Control for these values is luminal diameter at the lesion
site.

Abbreviation: n = number of arteries measured.

between cold pressor and nitroglycerin, was similar
for each group (21.5 \(\pm\) 15.6\%, 20.5 \(\pm\) 13.4\% and 26.4
\(\pm\) 14.1\% of control for groups 1, 2 and 3, respectively.

Alteration in luminal diameter at the site of fixed
atheromatous disease was observed with cold pressor
stimulation and nitroglycerin (table 3). Although the
mean changes were not statistically significant, the
luminal diameter in eight of 12 lesions (67\%) decreased
during the cold pressor test. After nitroglycerin, seven of 12 lesions (59\%) increased in
diameter.

Discussion

The diagnosis of coronary artery spasm is often
difficult. The likelihood of observing spontaneous coro-
nary artery spasm during coronary arteriography is
diminished because arteriographic observation is short, angiographic contrast media are vasodilators,
and subjects are routinely premedicated with nitro-
glycerin.18 Attempts to induce coronary artery spasm
with pharmacologic agents have been rewarding.
Ergot alkaloids,11,12 epinephrine in combination with
propranolol,13 and methacholine14 have been shown to
produce coronary artery spasm in patients with
variant angina. The ergot alkaloids appear to act
directly on vascular smooth muscle to produce
vasoconstriction.12 Epinephrine stimulates \(\alpha\)-adre-
nergic receptors in the coronary vascular bed and pro-
pranolol blocks the \(\beta\) receptors that cause vasodilata-
tion.13 Methacholine, a parasympathomimetic agent,
duces hypotension; Endo et al.14 suggested that coro-
nary artery spasm occurs as a result of reflex symp-
athetic stimulation secondary to the hypotension.
These pharmacologic agents may produce undesirable
side effects, particularly in patients with severe coro-
nary artery disease.

An easily performed and safe provocative test that
does not require the administration of pharmacologic
agents would be of value as a first line attempt to
provoke spasm, particularly in patients with coronary
artery disease. We believe that the cold pressor test
may offer this potential. The cold pressor test is
relatively simple to perform, and the response to cold
occurs rapidly (approximately 1 minute) and is readily
reversed by discontinuing the cold stimulus and ad-
ministering nitroglycerin. The arterial pressure
changes we observed were mild or moderate; however,
arterial pressure must be continuously monitored
because of the possibility of a exaggerated pressor
response.17, 18 Ventricular ectopy and ventricular
tachycardia — the only complications resulting from
the cold pressor test in our series — occurred in one
patient during the induced ischemia, but were readily
reversed after i.v. nitroglycerin. The safety of the test
is supported by studies that included patients with
critical multivessel atheromatous coronary artery dis-
ease.15, 19 We have, nevertheless, avoided using this
test in patients with left main coronary artery disease.

The cold pressor test has been used as a reflexogenic
stimulus for assessing cardiovascular reactivity.17
Cold pressor stimulation induces reflex vasoconstric-
tion of multiple vascular beds with a consequent in-
crease in peripheral vascular resistance and systemic
arterial blood pressure.20 The cold pressor test is
known to provoke angina19, 21 and has been shown to
reduce coronary blood flow in some patients with coro-
nary artery disease.15 Although the mechanism of
this response is not clear, reflex vasoconstriction of the
coronary vascular bed has been suggested.16

The present study shows that the cold pressor test
provokes generalized coronary vasoconstriction in
most patients and can provoke focal spasm of the coro-
nary vasculature in some. In our patients, focal
spasm occurred primarily in the vicinity of ath-
romatous disease. In two of seven patients, focal
spasm was associated with some manifestation of
myocardial ischemia. The hemodynamic response to
the cold pressor test is an increase in arterial blood
pressure.17, 20 hence, myocardial ischemia may result
from increased myocardial oxygen demand and does
not necessarily indicate coronary artery spasm.
Therefore, the angiographic demonstration of tran-
sient and reversible coronary artery narrowing is
necessary to implicate spasm. Both an increased
myocardial oxygen demand and a transiently diminished supply (spasm) probably contribute to ischemic manifestations in these patients.

The clinical significance of coronary artery spasm without myocardial ischemia, present in five of our patients, is unclear. We monitored only two limb leads during routine coronary arteriography; other leads, particularly precordial leads, might have revealed ischemic ST-segment changes. It is also possible that coronary spasm of insufficient severity or duration to produce myocardial ischemia can occur. The brevity of the cold pressor stimulus may limit its likelihood of provoking clinical manifestations of ischemia. We have seen patients with typical variant angina who had spontaneous coronary artery spasm during arteriography but who did not have concurrent chest pain or electrocardiographic abnormalities. Consequently, we speculate that the arteriographic demonstration of coronary artery spasm, even without associated ischemic manifestations, may indicate a pathophysiologic abnormality that could, at other times, produce myocardial ischemia.

The cold pressor test provoked coronary artery spasm in four of the six patients with variant angina and thus may be an important adjunct in detecting and documenting coronary spasm in this group of patients. In each of the four positive responders, the spasm developed at the site of an atheromatous plaque. Two patients with typical clinical manifestations of variant angina and normal coronary arteries did not manifest focal spasm during cold pressor stimulation. Thus, a negative cold pressor test does not exclude the diagnosis of variant angina. One of these patients responded to ergonovine; the other responded to neither cold pressor stimulation nor ergonovine maleate, but had been having frequent severe attacks and was given sublingual isosorbide dinitrate just before study, which may have prevented the occurrence of spasm.

Three patients did not have clinical evidence of variant angina, but manifested spasm during the cold pressor test. There is strong evidence that spasm may play a role in ischemic heart diseases other than variant angina. Reports of spasm in patients with classic angina,6 7 unstable angina6 9 and myocardial infarction10 support this possibility. Coronary artery spasm may superimpose on fixed atheromatous disease and patients may suffer the physiologic and clinical consequences of both; resting as well as exertional angina and ST-segment depression or elevation may be seen.6 Sympathetic stimuli, such as sudden standing, sexual intercourse, and other known angina provokers, may act partly by reflex or direct coronary artery spasm, as suggested by Sir William Osler 7 decades ago.22

The very definition of coronary artery spasm is unsettled. Although coronary artery spasm is regarded as a pathologic phenomenon, continuous alteration in vasomotor tone is a normal characteristic of arteries. Alterations in vasomotor tone are to a great extent influenced by the sympathetic nervous system. By stimulating the sympathetic nervous system, the cold pressor test can significantly alter coronary artery diameter, as shown in this study using quantitative arteriography. Further, coronary vasomotion was seen in patients with atypical chest pain and classic angina, as well as in those with variant angina. The distinction between normal coronary vasomotion and pathologic coronary artery spasm may be difficult and arbitrary. Rather, there appears to be a spectrum of vascular reactivity, with the coronary arteries of variant angina patients being more reactive (table 3). Nevertheless, coronary arteries that have atherosclerotic lesions are still capable of vasomotion in normal segments and at the lesion site, and normal or exaggerated vasomotion might further compromise the lumen. This process may occur more frequently than appreciated in patients with coronary atheromatous disease.

We did not evaluate the relative merits of the cold pressor stimulus and ergonovine maleate as provocative tests. Nonetheless, data were obtained in eight patients given both tests. Ergonovine maleate precipitated focal coronary spasm in one patient with variant angina who did not respond to cold pressor and produced more severe spasm in a group 2 patient with classic angina who responded to the cold pressor test. These findings suggest that ergonovine is a more potent provoker of coronary spasm. Ergonovine-induced spasm is associated with ischemic manifestations, sometimes to a frightening degree,23 and it is particularly helpful in evaluating the patient with chest pain suggestive of ischemia who has normal or insignificantly diseased coronary arteries. We avoid its use in patients with critical coronary artery lesions.

In this study, the cold pressor test precipitated coronary artery spasm with few complications. Although these results are encouraging, we cannot determine from this study what percentage of patients with coronary artery spasm can be identified by this approach. We recommend that the cold pressor test be tried before other pharmacologic attempts at provoking spasm, particularly in patients with coronary atherosclerotic disease. More extensive evaluation in larger groups of subjects under careful control observation is warranted before the efficacy of the test as a provocative maneuver can be established.

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