Comparative Sensitivity of Exercise, Cold Pressor and Ergonovine Testing in Provoking Attacks of Variant Angina in Patients with Active Disease

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SUMMARY Exercise, ergonovine and the cold pressor test have been used to provoke variant angina attacks. The sensitivity of these three tests was compared in 34 hospitalized patients with well documented, active variant angina who had recently undergone coronary arteriography. The three tests were performed on three consecutive days, and 28 of the 34 had the three tests within 1 week. Angina was provoked by ergonovine in all 34 patients, by exercise in 17 and by the cold pressor test in only five (p < 0.005). ST elevation developed during the ergonovine test in 32 (94%), during exercise in 10 (29%) and during the cold pressor test in only three (9%). With ergonovine, one patient had only ST depression and one had no ECG changes. During the cold pressor test two patients had pseudonormalization of abnormally negative T waves and 29 had no ECG changes. Exercise induced T-wave pseudonormalization in four patients, ST depression in nine others and no ECG changes in 11. ST elevation was more frequent with ergonovine than with either of the other tests (p < 0.0001). ST elevation or T-wave pseudonormalization occurred more often with exercise than with cold (p < 0.05), but both occurred less often than with ergonovine (p < 0.0001).

We conclude that the sensitivity of the ergonovine test is very high in patients with active variant angina and that exercise will provoke angina with ST elevation in about 30% of these cases. In contrast, the sensitivity of the cold pressor test is too low to be of much clinical value in the diagnosis of variant angina.

DIAGNOSING coronary artery spasm or variant angina is clinically important because specific treatment to prevent spasm relieves angina in most cases.1,2 However, spontaneous attacks are often difficult to document. For example, in a consecutive series of 162 variant angina patients who underwent coronary arteriography at our institution, only 32 had spontaneous spasm during the study.3 Similarly, coronary spasm occurred spontaneously during arteriography in 17 of the 107 variant angina patients reported by Maseri et al.4 The administration of ergonovine induces coronary spasm5-7 or transient ST elevation8,9 in almost all patients with active variant angina. Exercise testing has been reported to provoke angina and ST elevation in approximately 30% of variant angina patients;9,10 however, the incidence varies greatly, depending upon the underlying degree of disease activity.10 The cold pressor test provoked coronary spasm in four of six patients with variant angina in the study of Raizner et al.,11 but the sensitivity of this test has not been evaluated in a larger series.

This study was undertaken to compare the sensitivity of ergonovine, exercise and the cold pressor test in provoking attacks of variant angina. Each of the three tests was performed in a standardized fashion in 34 untreated hospitalized patients with well documented active variant angina.

Methods

Patient Population

The following criteria were required for the diagnosis of variant angina: burning or squeezing retrosternal chest pain at rest; relief of pain by sublingual nitroglycerin in less than 5 minutes; ST-segment elevation of at least 0.2 mV not present on the baseline ECG but documented during pain and disappearing after relief of pain; and no evidence of myocardial infarction.

The 34 study patients met these criteria, had recently undergone coronary arteriography (table 1) and were hospitalized in the coronary care unit with continuous electrocardiographic monitoring. Except for sublingual nitroglycerin given to relieve angina, the patients were receiving no cardiovascular drugs. Their mean age was 50.5 years (range 32–70 years); 30 were men and four were women. Three had multivessel disease, 16 had a one-vessel stenosis ≥70% and 15 had no lesions ≥70%, including three whose coronary arteries appeared normal. Left ventriculography was normal in 29 cases; a hypokinetic or akinetic zone was present in patients 6, 14, 28, 32 and 33. The baseline ECG was normal in 25 cases; patient 1 had minimal ST depression in leads V4 to V6, and eight patients had abnormally negative T waves (patients 5, 8, 11, 15, 25, 28, 32 and 33).

The site of ST elevation was the anterior ECG leads in 19 and the inferior leads in 15. The frequency of anginal attacks for each patient during the study period is listed in table 1. Asymptomatic episodes of transient ST elevation occurred in eight patients, all of whom were also experiencing frequent symptomatic attacks. In addition, nearly all patients had brief angina episodes that disappeared spontaneously or with nitroglycerin before electrocardiographic abnormalities could be detected. Both types of attacks were counted.
<table>
<thead>
<tr>
<th>Pt (years) Sex</th>
<th>Episodes of angina/day</th>
<th>Coronary arteriography</th>
<th>Ergonovine test</th>
<th>Cold pressor test</th>
<th>Exercise test</th>
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<td></td>
<td></td>
<td></td>
<td>Angina</td>
<td>Dose</td>
<td>ECG changes</td>
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<td>1 60 F</td>
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<td>LAD80</td>
<td>Yes</td>
<td>0.1</td>
<td>↑ V1-4</td>
</tr>
<tr>
<td>2 52 M</td>
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<td>LAD35, R40</td>
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<td>0.3</td>
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<tr>
<td>3 47 F</td>
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<td>Normal</td>
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<tr>
<td>4 52 M</td>
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<tr>
<td>5 48 M</td>
<td>2.3</td>
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<td>Yes</td>
<td>0.025</td>
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</tr>
<tr>
<td>6 42 M</td>
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<td>LAD90</td>
<td>Yes</td>
<td>0.05</td>
<td>↑ L, V3</td>
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<tr>
<td>7 42 M</td>
<td>9.3</td>
<td>R70</td>
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<td>0.05</td>
<td>↑ 2,3,F</td>
</tr>
<tr>
<td>8 65 M</td>
<td>2.0</td>
<td>LAD90, C50</td>
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<td>↑ V1-3</td>
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<tr>
<td>9 35 M</td>
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<td>10 68 M</td>
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<td>11 51 M</td>
<td>0</td>
<td>LAD70</td>
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<tr>
<td>12 58 M</td>
<td>1.8</td>
<td>C20</td>
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<td>15 52 M</td>
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<td>16 46 M</td>
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<td>18 43 M</td>
<td>1.3</td>
<td>D50, R70</td>
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<td>0.1</td>
<td>↑ V1-4</td>
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<td>0.3</td>
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<td>3.0</td>
<td>LAD75</td>
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<td>0.05</td>
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<td>3.0</td>
<td>Normal</td>
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<td>—</td>
<td>No</td>
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<td>LAD90, R70, C70</td>
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<td>↓ V3-4</td>
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<tr>
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<td>0.1</td>
<td>LAD45, R35, C60</td>
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<td>↑ 2,3,F</td>
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<tr>
<td>26 48 M</td>
<td>0.5</td>
<td>LAD35</td>
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<td>0.05</td>
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<tr>
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<td>0.3</td>
<td>Normal</td>
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<td>28 54 F</td>
<td>2.7</td>
<td>LAD30, R50</td>
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<tr>
<td>29 67 M</td>
<td>1.0</td>
<td>R80</td>
<td>Yes</td>
<td>0.1</td>
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<tr>
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<td>3.5</td>
<td>LAD65, C100</td>
<td>Yes</td>
<td>0.1</td>
<td>↑ V1-4</td>
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<td>31 62 M</td>
<td>0.4</td>
<td>R45</td>
<td>Yes</td>
<td>0.2</td>
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<td>4.0</td>
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<td>0.025</td>
<td>↑ V1-4</td>
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<td>33 44 F</td>
<td>1.4</td>
<td>LAD60, R90, C80</td>
<td>Yes</td>
<td>0.2</td>
<td>↑ 3, F</td>
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<td>34 56 M</td>
<td>0.3</td>
<td>LAD70</td>
<td>Yes</td>
<td>0.025</td>
<td>↑ 1, L, V1-3</td>
</tr>
</tbody>
</table>

Abbreviations: LAD = left anterior descending coronary artery; R = right coronary artery; C = circumflex; D = diagonal; ↑ = ST elevation; ▼ = ST depression; T pos = pseudonormalization of an abnormally negative T wave.
The mean number of attacks per day for the entire group was 2.2 ± 2.6 (range 0–12.0).

Study Design

All tests were performed between 10 a.m. and 4 p.m. to minimize bias due to circadian variations in disease activity. Where possible, one test was done on each of three consecutive days; however, extra days were required in many cases because of scheduling difficulties or postponement of a planned test because of a coincidental spontaneous attack. In 28 of the 34 patients, the three tests were completed within 1 week and in five of the remaining six patients within 2 weeks. The final patient was discharged before the third test (exercise) and returned for it 3 weeks later. The median interval for completing the test was 3 days and the mean was 5.4 days (range 2–29 days). The first test done was ergonovine in 14 patients, cold pressor in 12 and exercise in eight; the second test was ergonovine in nine, cold pressor in 14 and exercise in 11; the third test was ergonovine in 11, cold pressor in eight and exercise in 15. The order of tests was independent of the patient’s clinical status and was arranged according to the availability of personnel and the exercise test schedule. The test order was chosen at random when equally convenient choices were possible. Each patient gave written informed consent.

Only patients with known coronary anatomy were tested. An electrocardiographic lead was monitored continuously during each test. Cuff blood pressure and a 12-lead ECG were recorded before, at 1-minute intervals during, and for at least 5 minutes after each test. Three bipolar leads, CC5, CM4, and ML, were also recorded during exercise. The ergonovine tests were performed in the coronary care unit according to a protocol described in detail elsewhere. Briefly, i.v. boluses of ergonovine were administered at 5-minute intervals in the following sequence: 0.0125, 0.025, 0.05, 0.1, 0.2, 0.3 and 0.4 mg. The test was stopped and an i.v. bolus of 0.3 mg of nitroglycerin was given as soon as an ST-segment shift greater than 0.1 mV compared with the baseline tracing was detected. Exercise testing was performed on a treadmill using a Bruce protocol modified by adding a 3-minute warmup at 1.7 mph at a 5% grade, as described previously. The cold pressor test consisted of immersing the patient’s hand in ice water for 2 minutes.

No complications resulted from any of the 102 tests.

Data Analysis

A chi-square analysis was used to compare the results of the three tests. An unpaired t test was used to compare the frequency of spontaneous attacks in patients with and without exercise-induced ST elevation and in patients with ergonovine tests positive at high and low doses. Changes in arterial pressure or heart rate during each test were analyzed by paired t test. An analysis of variance was used to compare the differences in arterial pressure changes or heart rate changes among the three tests.

Results

The results of the three tests for each of the 34 patients are listed in table 1 and summarized in table 2. Figure 1 shows the ECG changes during the three tests for patient 13.

The ergonovine test provoked angina in all 34 patients and ST elevation in 32 (94%); one patient exhibited only ST depression and one had no ECG changes. The cold pressor test induced angina in only five of the 34 patients and only five had ECG changes: ST elevation in three (9%) and pseudonormalization of abnormally negative T waves in two. Angina occurred during exercise testing in 17 patients; 10 developed ST elevation (29%), four pseudonormalization of abnormally negative T waves, nine ST depression and 11 had no ECG changes. Thus, ST elevation occurred more often (p < 0.0001) with ergonovine than with either of the other two tests; the difference between the cold pressor and exercise tests is not statistically significant. Either ST elevation or pseudonormalization of T waves also occurred more often (p < 0.0001) with ergonovine than with the other two tests and more often with exercise than with the cold pressor test (p < 0.05).

The ECG site of ST elevation was the same during spontaneous and ergonovine-induced attacks in all cases. Likewise, electrocardiographic changes occurred in the expected leads in the five patients with a response to the cold pressor test. Patient 9 had exercise-induced ST elevation in the anterior leads and patient 28 had pseudonormalization of T waves in the anterior leads; in both cases spontaneous and ergonovine-induced attacks were characterized by ST elevation in the inferior leads.

The ergonovine test induced ST elevation at a low dose, 0.05 mg or less, in each of the five patients who had ECG changes during the cold pressor test (fig. 2). Four of these five patients had the same type of ECG change during exercise as during the cold pressor test, ST elevation in two and T-wave pseudonormalization in two.

One patient (no. 24) had exercise-induced ST elevation, but developed ST depression during the ergonovine test. Each of the 13 other patients with exercise-induced ST elevation or T-wave pseudonormalization...

| TABLE 2. Comparison of ECG Changes During Ergonovine, Cold Pressor and Exercise Tests |
|---------------------------------|---------------------------------|---------------------------------|
|                                  | Ergonovine test             | Cold pressor test          | Exercise test              |
| ST elevation                    | 32 (94%)                   | 3 (9%)                      | 10 (29%)                   |
| Pseudonormalization of T waves  | 0                           | 2                            | 4*                          |
| ST depression                   | 1                           | 0                            | 9†                          |
| No ECG changes                  | 1                           | 29                           | 11                          |
| Total                           | 34                          | 34                           | 34                          |

*two of these four patients also had ST depression.
†Six of these nine patients had organic stenoses ≥50%.
had ST elevation during the ergonovine test, 10 at a
dose of 0.05 mg or less.

Patients with ST elevation during the exercise test
experienced more spontaneous attacks per day than
the remainder of the study patients (4.0 ± 3.8 vs 1.4 ±
1.4, p < 0.05). Spontaneous attacks also occurred
more often in patients with a positive ergonovine test at
a dose of 0.05 mg or less than in those positive at
higher doses (3.0 ± 3.2 vs 1.2 ± 1.4, p < 0.05).

Figure 3 illustrates the changes in arterial pressure
and heart rate from just before the test to either just
before the onset of angina or to the end of the test if no
angina occurred. Heart rate increased from 69.3 ±
13.3 to 74.0 ± 11.2 beats/min (p < 0.001) with
ergonovine and from 72.0 ± 14.1 to 78.9 ± 15.3
beats/min (p < 0.001) during the cold pressor test.
Systolic (p < 0.001) and diastolic (p < 0.01) arterial
pressure increased during each of the three tests. The
increase in systolic pressure was greater during exercise
during than during the cold pressor test (142 ± 20 to 191
± 29 vs 133 ± 18 to 165 ± 31 mm Hg, p < 0.025)
and the increase during the cold pressor test was in turn
greater than during the ergonovine test (139 ± 21 to
151 ± 23 mm Hg, p < 0.001).

Discussion

This study demonstrates that in patients with active
variant angina, an attack can be provoked by ergono-
vine in more than 90% of cases, by exercise in approx-
imately 30% and by the cold pressor test in about 10%.
The relevance of these findings to clinical practice is
influenced by the following considerations.

First, the degree of disease activity affects the sensi-
tivity of both ergonovine13-15 and exercise10 testing and
probably also affects the sensitivity of the cold pressor
test. Provocative testing is most useful in patients with
infrequent spontaneous attacks, where the diagnosis
cannot be made by other means. In such cases, the
sensitivity of the tests would probably be lower than in
this study. Spontaneous variations in disease activity
occur frequently in patients with coronary spasm, and
during periods of disease inactivity, provocative testing
may yield negative results.15

A second limitation of this study is that the end point
of the tests is ECG changes and not the direct visualiza-
tion of coronary spasm. Coronary spasm may occur in
the absence of ECG changes or in association with
abnormalities less specific than ST elevation.4 During
transient ST elevation in variant angina, coronary
spasm is invariably present.4,7,16 In our experience, T-
wave pseudonormalization after ergonovine adminis-
tration is also highly specific for coronary spasm, but
this correlation has never been documented in a large
series of patients. The specificity of this ECG finding
for coronary spasm during exercise has not been sys-
tematically studied. ECG changes during exercise are
usually caused by an increase in myocardial oxygen
demand; however, in the absence of previous myocar-
dial infarction, exercise-induced ST elevation is spe-
cific for coronary spasm.17,18 Thus, the presence of
coronary spasm can be inferred when ST elevation
occurs during any of the three provocative tests and
can be suspected with pseudonormalization of abnor-
mally negative T waves. ST depression is a nonspecif-

FIGURE 1. Results of the three tests in patient 13. The control ECG is normal. Ergonovine induced ST elevation
in leads 2, 3 and aVF, at a dose of 0.05 mg. The next day, neither angina nor ECG changes occurred during the cold
pressor test. Three days later, during the exercise test, angina developed with ST elevation in leads 2, 3 and aVF.
ECG changes had ST elevation.

**FIGURE 2.** The number of patients with ST elevation at each dose level during the ergonovine test. The five patients with ECG changes during the cold pressor test (black columns) all had ST elevation at a dose of 0.05 mg or less during the ergonovine test. The hatched columns represent patients who had exercise-induced ST elevation and no ECG changes during the cold pressor test.

The finding during provocative testing, and coronary arteriography is necessary to define its cause. With the exception of exercise, provocative tests usually do not induce isolated ST depression in patients with active variant angina, as shown by the results of this study.

Would sensitivity have increased substantially, particularly for the cold pressor test, if it had been performed during coronary arteriography? The absence of angina in 29 of the 34 patients during the cold pressor test does not eliminate the possibility that coronary spasm was present. Among the four variant angina patients with cold-induced coronary spasm studied by Raizner et al., ST elevation was observed in only two; however, only leads I and III were monitored, and the two patients without ECG changes had left anterior descending coronary spasm. We have performed cold pressor tests during arteriography in five patients with active variant angina; coronary spasm occurred in only one instance and was associated with ST elevation. This patient’s positive response may have been coincidental; he was in a very active phase of his disease and also had a spontaneous episode of spasm during arteriography. These findings suggest that the sensitivity of the cold pressor test is indeed low, even during coronary arteriography.

The cold pressor test has been suggested as a promising alternative to ergonovine administration because it acts through intrinsic reflex mechanisms and, thus, may be safer. However, it is likely that equivalent degrees of coronary spasm are equally dangerous, irrespective of the cause. Ergonovine can induce irreversible coronary obstruction, resulting in death or transmural infarction. Myocardial infarction has also been reported as a complication of the cold pressor test.

The clinical and angiographic features of the patients with a positive cold pressor test were similar to those of the entire group (table 1). However, these patients were characterized by the ease with which attacks could be provoked by other stimuli; all five had ST elevation at an ergonovine dose of 0.05 mg or less, and four of five had ST elevation or T-wave pseudo-normalization with exercise.

Patients who developed ST elevation in response to exercise or low doses of ergonovine tended to have more spontaneous attacks, as noted in previous studies, but exceptions to this trend were frequent and the groups overlapped widely.

This study was specifically designed to compare the sensitivities of three provocative tests. For such a comparison to be accurate, the same patients should be used to assess each test and the tests should be done in

**FIGURE 3.** Systolic (p < 0.001) and diastolic (p < 0.01) arterial pressure and heart rate (p < 0.001) increased during each of the three tests. The increase in systolic pressure during exercise was greater than during the cold pressor test (p < 0.025) and the increase during the cold pressor test was greater than during the ergonovine test (p < 0.001).
a variable order over a short time to limit potential bias due to spontaneous changes in disease activity. These conditions would be difficult to fulfill if coronary arteriography were repeated during each test.

The specificity of these provocative tests were not assessed in this study. In patients without symptoms due to coronary spasm, both ergonovine and cold increase coronary resistance and decrease coronary diameter; this action or the increased afterload may cause angina if severe organic stenoses are present. The border between coronary spasm and "physiologic" increases in coronary tone is difficult to define, both may cause angina, ECG changes and a transient increase in a focal stenosis. As shown in table 1 and as noted previously, the response to provocative tests in variant angina does not correlate with the presence or severity of organic stenoses.

Each of the three provocative tests increased arterial pressure; the increase induced by ergonovine in this study was less than with cold, which was less than during exercise. In patients with a positive response to more than one test, the arterial pressure and pressure-rate product at the onset of angina and electrocardiographic abnormalities was highly variable. In contrast to stable angina where the ischemic threshold is fixed and reproducible, the hemodynamic response to the provocative tests does not seem to correlate with their potential to induce spasm. Similarly, De Servi et al. demonstrated that the angina threshold may be highly variable when exercise tests are repeated in patients with variant angina. There is no evidence to suggest that increases in myocardial oxygen demand play a role in the induction of variant angina with provocative tests.

From a practical point of view, the results of this study indicate that even in patients with active variant angina, the cold pressor test rarely provokes an attack, and is thus of little diagnostic value. In contrast, the sensitivity of the ergonovine test in the same population was greater than 90%, using ST elevation as the criterion for a positive response.

References


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D D Waters, J Szlachcic, R Bonan, D D Miller, F Dauwe and P Theroux

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