Exercise Testing in Patients with Variant Angina: Results, Correlation with Clinical and Angiographic Features and Prognostic Significance

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SUMMARY Eighty-two patients with variant angina underwent a treadmill exercise test using 14 ECG leads, and 67 also underwent exercise thallium-201 scans. The test induced ST elevation in 25 patients (30%), ST depression in 21 (26%) and no ST-segment abnormality in 36 (44%). ST elevation during exercise occurred in the same ECG leads as during spontaneous attacks at rest, and was always associated with a large perfusion defect on the exercise thallium scan. In contrast, exercise-induced ST depression often did not occur in the leads that exhibited ST elevation during episodes at rest. The ST-segment response to exercise did not accurately predict coronary anatomy: Coronary stenoses ≥ 70% were present in 14 of 25 patients (56%) with ST elevation, in 13 of 21 (62%) with ST depression and in 14 of 36 (39%) with no ST-segment abnormality (NS). However, the degree of disease activity did correlate with the result of the exercise test: ST elevation occurred during exercise in 11 of 14 patients who had an average of more than two spontaneous attacks per day, in 12 of 24 who had between two attacks per day and two per week, and in only two of 31 who had fewer than two attacks per week (p < 0.005). ST elevation during exercise was reproducible in five of five patients retested during an active phase of their disease, but not in three of three patients who had been angina-free for at least 1 month before the repeat test. Twelve patients with exercise-induced ST elevation were retested during treatment with calcium antagonist drugs; in 10 of 12, ST elevation did not occur with the second test. During a mean follow-up of 20.3 ± 14.5 months, death or myocardial infarction occurred in three of the 25 patients with ST elevation during exercise, none of 21 with ST depression and two of 36 with no ST abnormality.

We conclude that in variant angina patients, the results of an exercise test correlate well with the degree of disease activity but not with coronary anatomy, and do not define a high-risk subgroup.

ALTHOUGH not described by Prinzmetal et al. in their original paper,1 exercise-induced angina with ST elevation has been reported in many patients with otherwise typical variant angina.2-27 Because most of these studies deal with isolated or selected cases, the frequency of this finding in patients with variant angina and its clinical importance are difficult to ascertain.

The significance of ST depression during exercise in variant angina is also unclear. Coronary artery spasm may cause ST elevation during exercise in patients with variant angina;20, 21 however, exercise-induced ST depression in these patients is usually attributed to fixed coronary lesions,22 although coronary artery spasm at rest can cause either ST-segment depression or elevation.19 Yasue et al.28 reported that coronary spasm causes ST depression during exercise in some patients without rest angina.

Between 1976 and 1980, 130 patients were hospitalized at our institution because of active variant angina. Eighty-two patients underwent treadmill exercise testing using 14 electrocardiographic leads; in 67 of the 82 patients, thallium perfusion scans were also done during exercise.

Methods

Patient Population

The following criteria were required for the diagnosis of variant angina: burning or squeezing retrosternal chest pain at rest; sublingual nitroglycerin always relieved the pain 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.

Between 1976 and 1980, 130 patients who fulfilled these criteria were hospitalized at our institution. Exercise testing was not performed in 48 of these patients because of recent myocardial infarction or myocardial infarction during hospitalization in 19 patients, recent coronary bypass in four, aortic valve disease in two, severe claudication in two, arterial complications after coronary arteriography in two, very active variant angina (more than 10 attacks per day off treatment) in five, multiple, critical fixed coronary lesions in three, difficulty in scheduling the test before the beginning of treatment in 10 and a cerebrovascular accident in one patient.

Exercise Testing

Tests were performed during mid-morning to eliminate variability due to circadian rhythms.22 Drugs that might affect the results of the exercise test were discontinued for an appropriate interval before the test. All patients were exercised using a Bruce protocol,23

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modified by adding a 3 minute warm-up at 1.7 mph at a 5% grade.30-32 Briefly, cuff blood pressure, a standard 12-lead ECG (excluding aVR) and leads CC5, CM4 and ML were recorded each minute during exercise and for 5 minutes thereafter. End points were angina in 30 patients, incapacitating fatigue or dyspnea in 39, complex ventricular arrhythmias in one patient, claudication in one patient, attainment of 100% of age-predicted maximal heart rate in five patients, and an ST-segment shift of 3 mm or more compared with the resting ECG in six. Criteria for significant ST-segment depression were horizontal or downsloping ST-segment depression of 0.1 mV or more for 0.08 second in any lead compared with the resting ECG or slowly upsloping ST-segment depression 0.2 mV or greater at 0.08 second after the J point.91 ST-segment elevation was measured 0.04 second after the J point and was considered significant in any lead if the ECG showed 0.1 mV or more elevation compared with the resting tracing. Three consecutive complexes conforming to one of these criteria were required for a test to be considered abnormal.

In 67 of the 82 patients, 2 mCi of thallium-201 were injected intravenously 1 minute before the end of exercise. Within 30 minutes of this injection, a gamma camera recorded left anterior oblique, antero-posterior and lateral views, which were compared with resting thallium-201 scans. In 15 patients with normal reperfusion scans 4 hours after exercise, a separate resting thallium scan was not done. Reperfusion scans were not routinely recorded in the other patients. All thallium scans were interpreted independently by the same observer unaware of the results of the coronary arteriogram and exercise test.

Eight of the patients with exercise-induced ST elevation were retested when taking no drugs. The selection of these patients was not done in a randomized fashion, but depended upon laboratory and patient availability during intervals while not taking drug treatment; however, the clinical and angiographic features of the retested patients are similar to those of the entire group. The interval between the two tests was 1 day in two patients, 4 months in three and 20 months in three. Twelve patients with exercise-induced ST elevation were also retested during treatment: five with nifedipine, five with diltiazem and two with a combination of both drugs. The dosages were 20 mg orally every 6 hours for nifedipine and 120 mg orally every 8 hours for diltiazem.

Angiographic Studies

During hospitalization, selective coronary arteriography was performed by a percutaneous transfemoral approach using preformed polyethylene catheters.94 Cranio-caudal and caudocranial sagittally angulated views of the left coronary artery were routinely filmed.94 Patients were not routinely given nitroglycerin before angiography, but if coronary stenoses were present, the involved vessels were restudied in multiple views after nitroglycerin administration. Ergonovine was not routinely administered to induce coronary spasm during angiography.38

The left ventricle was opacified and filmed in the 30° right anterior oblique view. Wall motion abnormalities were evaluated qualitatively using standard terminology.97

Statistical Analysis

A chi-square test was used to assess the statistical significance of intergroup differences for noncontinuous variables. Intergroup differences for continuous variables were assessed using an analysis of variance. Values are mean ± SD.

Results

During the exercise test, ST elevation was induced in 25 patients (30%), ST depression in 21 (26%) and no ST-segment shifts in 36 (44%).

ST Elevation

The data for the patients who developed ST elevation during exercise are summarized in table 1. Angina accompanied ST elevation in 20 of the 25 patients with this finding. In 24 of the 25, the electrocardiographic site of ST elevation during exercise was the same as during spontaneous variant angina attacks at rest — anterior in 15 and inferior in nine. ST elevation began during exercise in all patients in this group, although in most cases maximal ST elevation occurred within 1 minute after the test was stopped. All ST segments returned to baseline within 5 minutes. ST depression was detected before ST elevation during exercise in only one patient. The average maximal height of ST elevation was 3.7 mm (range 1–10 mm). Coincident with ST elevation, ST depression occurred in other leads in 20 of the 25 patients.

Thallium-201 scans were done with exercise in 22 of the 25 patients, and in each case a large, clear-cut zone of hypoperfusion was detected in the area corresponding to the electrocardiographic site of ST elevation. Control scans at rest were normal in 19 of these 22 patients and showed smaller or fewer defects in the other three. None of the 17 patients with thallium scans who had ST depression coexisting with ST elevation had a second perfusion defect corresponding to the site of ST depression.

At coronary arteriography, 11 of the 25 patients with ST elevation during exercise had no fixed coronary lesions ≥ 70%, 10 had one-vessel disease, three had two-vessel and one had three-vessel disease. Spontaneous spasm developed during arteriography in seven patients, always in the artery corresponding to the site of ST elevation and the thallium defect. Left ventriculography was normal in 21 of the patients; three had an akinetic and one had a hypokinetic segment, in each case distal to a coronary lesions ≥ 70%.

Eight of the 25 patients were retested while not taking medication. In five of the eight, ST elevation occurred during the second test, in the same ECG leads as during the first test. Each of these five patients still had spontaneous episodes of variant angina at the time of the second test. In the other three patients, no spontaneous attacks had been reported for at least 1 month before the second test and none were being
treated with cardiac medication. Two of these patients developed no angina or ST abnormalities during the second test, despite longer treadmill times, higher heart rates and higher pressure-rate products. The third patient in this group developed ST depression during the second test, attributable to severe fixed coronary lesions.

Twelve of the patients underwent another exercise

### Table 1. Coronary Arteriographic and Exercise Test Data for Patients with ST Elevation During Exercise

<table>
<thead>
<tr>
<th>Pt</th>
<th>Coronary arteriography (% stenosis)</th>
<th>LV angiography</th>
<th>Spontaneous ST elevation</th>
<th>Exercise test results</th>
<th>Thallium scans</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Normal</td>
<td>Normal</td>
<td>V2-5</td>
<td>aV1, V2-4</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>RCA 40%</td>
<td>Normal</td>
<td>2,3,aVF</td>
<td>2,3,aVF, ML</td>
<td>aV1</td>
</tr>
<tr>
<td>3</td>
<td>LAD 40%</td>
<td>Normal</td>
<td>1,aVL, V1-4</td>
<td>2,3,aVF, ML</td>
<td>aV1, V1-5, CM5</td>
</tr>
<tr>
<td>4</td>
<td>LAD 40%</td>
<td>Normal</td>
<td>1,aVL, V1-6</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>RCA 35%</td>
<td>Normal</td>
<td>2,3,aVF, V5-6</td>
<td>2,3,aVF, ML</td>
<td>aV1, V2</td>
</tr>
<tr>
<td>6</td>
<td>Normal</td>
<td>Normal</td>
<td>2,3,aVF</td>
<td>2,3,aVF, ML</td>
<td>aV1, V4-6, CM5</td>
</tr>
<tr>
<td>7</td>
<td>LAD 60%, Cx 65%</td>
<td>Normal</td>
<td>V1-4</td>
<td>V1-2</td>
<td>2,3,aVF,ML</td>
</tr>
<tr>
<td>8</td>
<td>LAD 60%</td>
<td>Normal</td>
<td>V1-4</td>
<td>1,aVL, V1-5, CM5</td>
<td>2,3,aVF,ML</td>
</tr>
<tr>
<td>9</td>
<td>LAD 50%, RCA 70%</td>
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<td>2,3,aVF</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>LAD 60%, RCA 70%</td>
<td>Normal</td>
<td>1,aVL, V2-5</td>
<td>V2</td>
<td>V5-6, CM5, CM5, ML</td>
</tr>
<tr>
<td>11</td>
<td>RCA 60%</td>
<td>Normal</td>
<td>2,3,aVF</td>
<td>2,3,aVF, ML</td>
<td>1,aVL, CC5</td>
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<tr>
<td>12</td>
<td>LAD 75%</td>
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<td>1,2,3,aVF, aVF1-6, aVF1-6</td>
<td>V1-1, CC5</td>
<td>2,3,aVF, ML</td>
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<td>2,3,aVF,ML</td>
<td>1,aVL, CC5</td>
</tr>
<tr>
<td>14</td>
<td>LAD 75%, Cx 100%, RCA 100%</td>
<td>Post. basal AK</td>
<td>V1-4</td>
<td>V2-4</td>
<td>V5-6, CM5, CM5</td>
</tr>
<tr>
<td>15</td>
<td>LAD 70%</td>
<td>Normal</td>
<td>1,aVL, V1-6</td>
<td>aV1, V1-3</td>
<td>2,3,aVF, V5, 3,aVF, CM5, CM5, ML</td>
</tr>
<tr>
<td>16</td>
<td>LAD 70%</td>
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<td>V1-4</td>
<td>V1-5, CM5</td>
<td>3,aVF</td>
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<tr>
<td>17</td>
<td>LAD 90%, Cx 50%</td>
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<td>1,aVL, V1-6</td>
<td>aV1, V1-4</td>
<td>3,aVF, ML</td>
</tr>
<tr>
<td>18</td>
<td>LAD 75%, RCA 40%</td>
<td>Ant. lat. AK</td>
<td>V1-5</td>
<td>aV1, V1-6, CC5</td>
<td>2,3,aVF, ML</td>
</tr>
<tr>
<td>19</td>
<td>LAD 90%</td>
<td>Apical HK</td>
<td>aV1, V1-3</td>
<td>V1-2</td>
<td>2,3,aVF, V5-6, CC5, CM5, ML</td>
</tr>
<tr>
<td>20</td>
<td>LAD 50%, Cx 75%, RCA 90%</td>
<td>Normal</td>
<td>2,3,aVF</td>
<td>2,3,aVF,ML</td>
<td>aV1, V2</td>
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<tr>
<td>21</td>
<td>LAD 80%, RCA 50%</td>
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<td>V1-4</td>
<td>V1-5, CC5</td>
<td>2,3,aVF,ML</td>
</tr>
<tr>
<td>22</td>
<td>C90%, RCA 100%</td>
<td>Inf. post. basal AK</td>
<td>V1-3</td>
<td>2,3,aVF,ML</td>
<td>No</td>
</tr>
<tr>
<td>23</td>
<td>RCA 75%</td>
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<td>2,3,aVF, V5-6</td>
<td>2,3,aVF, V5-6</td>
<td>aV1</td>
</tr>
<tr>
<td>24</td>
<td>LAD 70%, RCA 50%</td>
<td>Normal</td>
<td>V1-4</td>
<td>aV1, V1-2</td>
<td>CM5</td>
</tr>
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<td>25</td>
<td>RCA 20%</td>
<td>Normal</td>
<td>2,3,aVF</td>
<td>ML</td>
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</table>

Abbreviations: LAD = left anterior descending coronary artery; Cx = circumflex artery; RCA = right coronary artery; AK = akinesia; HK = hypokinesia; HRmax = maximal heart rate (beats/min); LV = left ventricular.
test: five during treatment with nifedipine, five with diltiazem, and two with a combination of both drugs. Eight of the 12 had no ST-segment abnormality during the second test, despite equivalent or longer treadmill times in all eight and higher pressure-rate products in five. Each of these eight patients had a large perfusion defect on the thallium scan during their first test and a normal scan at rest. During the repeat exercise test with treatment, five of the patients had normal thallium scans and three had smaller perfusion defects than in their initial test. Two of these three had a fixed coronary stenosis > 70% to account for the defect.

Two of the patients with ST elevation during their first test developed ST depression during their repeat test on treatment; in both instances, the ST depression could be attributed to fixed coronary stenoses > 70%. Two patients showed ST elevation during the second test despite treatment. Both had large thallium defects during both tests; neither had a critical coronary stenosis or left ventricular contraction abnormality to explain the persistence of exercise-induced ST elevation. Eleven of the 12 patients had no spontaneous attacks of variant angina during treatment; the one exception was one of the two patients whose ST elevation recurred during the repeat test.

**ST Depression**

In 21 of the 82 patients tested, ST depression developed during or immediately after exercise, in the absence of ST elevation. The data for these patients are listed in table 2. Angina occurred during 10 of these 21 tests, compared with 20 of the 25 with ST elevation. The electrocardiographic leads that showed ST depression did not correlate well with the leads where ST elevation occurred during spontaneous variant angina attacks. For example, ST depression included the inferior leads in only five of the 10 patients whose ST elevation at rest occurred in this region.

At coronary arteriography, two of the 21 patients in this group had three-vessel disease, two had two-vessel disease, nine had one vessel disease and eight had no coronary stenosis ≥ 70%, including five with five no stenosis ≥ 50%. Left ventriculography was normal in 14 patients, revealed a hypokinetic segment in one

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**Table 2. Coronary Arteriographic and Exercise Test Data for Patients with ST Depression During Exercise**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Coronary arteriography (% stenosis)</th>
<th>LV angiography</th>
<th>Spontaneous ST elevation</th>
<th>Exercise test results</th>
<th>Thallium scans</th>
</tr>
</thead>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>ST depression</td>
<td>Angina HRmax</td>
</tr>
<tr>
<td>1</td>
<td>LAD 35%, RCA 40%</td>
<td>Normal</td>
<td>V2-3</td>
<td>V4-6,CC5,CM5</td>
<td>No 176</td>
</tr>
<tr>
<td>2</td>
<td>Normal</td>
<td>Normal</td>
<td>2,3,aVF</td>
<td>CC5,CM5</td>
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<td>3</td>
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<td>Normal</td>
<td>V1-4</td>
<td>CC5,CM5</td>
<td>No 149</td>
</tr>
<tr>
<td>4</td>
<td>Normal</td>
<td>2,3,aVF</td>
<td>2,3,aVF;CM5,ML</td>
<td>Yes 122</td>
<td>Normal</td>
</tr>
<tr>
<td>5</td>
<td>LAD 90%, RCA 90%</td>
<td>Ant. lat. AK</td>
<td>2,3,aVF</td>
<td>2,3,aVF;CM5,ML</td>
<td>No 157</td>
</tr>
<tr>
<td>6</td>
<td>LAD 60%, Cx 70%</td>
<td>Normal</td>
<td>V1-3</td>
<td>2,3,aVF;V3-6,CC5,CM5,ML</td>
<td>Yes 137</td>
</tr>
<tr>
<td>7</td>
<td>LAD 70%, Cx 90% RCA 90%</td>
<td>Ant. lat. HK</td>
<td>2,3,aVF</td>
<td>2,3,aVF;V3-6,CC3,CM5,ML</td>
<td>Yes 136</td>
</tr>
<tr>
<td>8</td>
<td>RCA 80%</td>
<td>Normal</td>
<td>2,3,aVF</td>
<td>V5-6,CC5,CM5</td>
<td>Yes 114</td>
</tr>
<tr>
<td>9</td>
<td>LAD 90%, Cx 50%</td>
<td>Ant. AK</td>
<td>1,aVL;V2-5</td>
<td>V5-6,CC5,CM5</td>
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<td>10</td>
<td>LAD 100%, Cx 90%, RCA 80%</td>
<td>Ant. lat. AK</td>
<td>V1-5</td>
<td>CM5,ML</td>
<td>No 104</td>
</tr>
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<td>11</td>
<td>LAD 30%</td>
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<td>V1-3</td>
<td>V5-6,CC5,CM5</td>
<td>No 144</td>
</tr>
<tr>
<td>12</td>
<td>Cx 90%, RCA 95%</td>
<td>Normal</td>
<td>2,3,aVF</td>
<td>V3-6,CC5,CM5,ML</td>
<td>Yes 146</td>
</tr>
<tr>
<td>13</td>
<td>LAD 80%, C 60%</td>
<td>Normal</td>
<td>V1-4</td>
<td>V4-6,CM5</td>
<td>No 121</td>
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<tr>
<td>14</td>
<td>LAD 50%, Cx 60%</td>
<td>Normal</td>
<td>2,3,aVF</td>
<td>2,3,aVF;CM5,ML</td>
<td>No 89</td>
</tr>
<tr>
<td>15</td>
<td>LAD 50%, RCA 100%</td>
<td>Inf. AK</td>
<td>V1-2</td>
<td>V5-6,CC5,CM5</td>
<td>Yes 112</td>
</tr>
<tr>
<td>16</td>
<td>LMCA 30%</td>
<td>Normal</td>
<td>2,3,aVF</td>
<td>2,3,aVF,ML</td>
<td>No 132</td>
</tr>
<tr>
<td>17</td>
<td>LAD 50%, RCA 95%</td>
<td>Inf. AK</td>
<td>2,3,aVF</td>
<td>V4-6,CC5,CM5</td>
<td>No 118</td>
</tr>
<tr>
<td>18</td>
<td>LAD 55%</td>
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<td>aVL,V2-3</td>
<td>CM5,ML</td>
<td>Yes 153</td>
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<tr>
<td>19</td>
<td>RCA 80%</td>
<td>Normal</td>
<td>2,3,aVF</td>
<td>CC5,CM5</td>
<td>Yes 102</td>
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<tr>
<td>20</td>
<td>LAD 50%, Cx 50% RCA 80%</td>
<td>Inf. AK</td>
<td>2,3,aVF</td>
<td>V4-6,CC5,CM5</td>
<td>Yes 112</td>
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<td>21</td>
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<td>V1-4</td>
<td>2,3,aVF;V5-6,CM5,ML</td>
<td>No 169</td>
</tr>
</tbody>
</table>

Abbreviations: LAD = left anterior descending coronary artery; C = circumflex; RCA = right coronary artery; LMCA = left main coronary artery; AK = akinesis; HK = hypokinesis.
patient and akinetic segments in six patients. Each abnormal segment was associated with a coronary stenosis \( \geq 70\% \).

The results of the exercise thallium scan in this group was helpful in predicting the presence of fixed coronary lesions. All five of the patients with normal rest and exercise scans had no coronary stenosis \( \geq 70\% \). Two patients had a defect on the resting scan that did not change during exercise; both had one-vessel disease. Of the 11 patients with a hypoperfused region on the exercise scan but not at rest, two had multivessel disease, six had one-vessel disease and three had no stenosis \( \geq 70\% \), including two with no stenosis \( \geq 50\% \). Three of the 21 patients in this group, all with fixed lesions, did not undergo thallium scanning. The data for one of the five patients with exercise-induced ST depression but with a normal thallium scan are illustrated in figure 1.

No ST-segment Shifts

No ST-segment abnormalities appeared during exercise testing in 36 of the 82 patients. Seven of these 36 patients complained of angina during the test. None of the 36 patients had three-vessel disease, five had two-vessel disease, nine had one-vessel disease and 22 had no stenosis \( \geq 70\% \). Left ventriculography was normal in 30 of the 36, showed a akinetic segment in one patient with normal coronary arteries and hypokinesis in five patients, including one with no significant coronary lesions.

Thallium scans were done in conjunction with the exercise test in 27 of the 36 patients. Of the 20 with no stenoses \( \geq 70\% \) who were evaluated with perfusion scans, 19 had normal studies and one had a small exercise defect not present at rest; her coronary arteries were normal, but she had complained of angina during the test. Of the seven patients with fixed lesions who had perfusion scans, only two showed a perfusion defect during exercise; the other five all had one-vessel disease.

The failure of exercise to induce ST depression or perfusion abnormalities in some patients in this group with fixed coronary lesions could be explained by an inadequate work load; the maximal heart rate attained

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** (top) ECG tracings at rest (left panels) and during exercise (right panels) from a patient with variant angina (no. 14, table 2) whose spontaneous ST elevation at rest occurred in leads 2, 3 and aVF. Single coronary stenoses of only 50% were present in the circumflex and left anterior descending coronary arteries. Exercise was terminated at the end of the fifth minute at a heart rate of 89 beats/min because of up to 4 mm of ST depression in leads 2, 3, aVF, V2-V6, CC5, CM5 and ML. (bottom) The exercise thallium scans for this patient are normal. The cause of ST depression during exercise in this instance is uncertain. AP = anteroposterior; LAO = left anterior oblique.
by six of the 14 with fixed lesions but no ST abnormality was less than 140 beats/min.

Clinical Correlations

Table 3 is a comparison of the clinical, angiographic and exercise test measurements among the patients with exercise-induced ST elevation, ST depression and no ST abnormalities. The age and sex distributions within the three groups are similar. The site of ST elevation during attacks at rest was more often anterior than inferior in the patients with exercise-induced ST elevation compared to the other two groups; but this difference was small and not statistically significant.

The prevalence of effort angina was also compared among the three groups. Effort angina was diagnosed if angina occurred during physical exertion, even if it was variable and not reproducible; in most patients, effort angina was difficult to evaluate because it was overshadowed by frequent attacks of angina at rest. The prevalence of effort angina was almost identical in the three groups, approximately 60% (table 3). The presence of effort angina also correlated poorly with the presence of fixed coronary lesions; 26 of 41 patients with stenoses of 70% or greater had effort angina, compared with 22 of the 41 without stenoses of 70% or greater.

The clinical characteristic that correlated best with the result of the exercise test was the degree of disease activity. Eleven of the 14 patients with more than two attacks of variant angina per day without treatment showed ST elevation during exercise, one patient had ST depression and two patients had no ST abnormality. Among the 24 patients with two or more attacks per week but two or less per day, 12 developed ST elevation, eight ST depression and four no ST-segment shift. Only two of the 31 patients with fewer than two attacks per week had ST elevation during exercise; seven had ST depression and 22 had no ST abnormality. The differences between groups were statistically significant (p < 0.005). The underlying disease activity could not be assessed in 13 of the 82 patients because they were receiving calcium-antagonist drugs within the 2 weeks before the exercise test.

The ST-segment response to exercise was of little value in predicting the coronary anatomy. Eleven of 25 patients (44%) with ST elevation, eight of 21 (38%) with ST depression and 22 of 36 (61%) with no ST abnormality had no coronary stenosis ≥ 70% (NS). One-vessel and multivessel disease were also relatively evenly distributed among the three groups.

Although wide overlap existed among the three groups, the mean treadmill time in patients with no ST abnormalities exceeded that in patients with ST depression, which was in turn higher than in patients with ST elevation. The mean maximal heart rates and pressure-rate products for the three groups showed a trend in the same direction (table 3), but the differences were not statistically significant. Ventricular arrhythmias occurred during or immediately after exercise in five of the 36 (14%) with no ST abnor-

Table 3. Clinical Characteristics of Variant Angina Patients Classified According to ST-segment Response to Exercise

<table>
<thead>
<tr>
<th></th>
<th>ST elevation</th>
<th>ST depression</th>
<th>No ST abnormality</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pts</td>
<td>25</td>
<td>21</td>
<td>36</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.2 ± 8.7</td>
<td>52.1 ± 9.8</td>
<td>49.8 ± 9.2</td>
<td>NS</td>
</tr>
<tr>
<td>Male/female</td>
<td>21/4</td>
<td>13/8</td>
<td>24/12</td>
<td>NS</td>
</tr>
<tr>
<td>Effort angina</td>
<td>15 (60%)</td>
<td>13 (62%)</td>
<td>20 (56%)</td>
<td>NS</td>
</tr>
<tr>
<td>Site of ST elevation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>15</td>
<td>10</td>
<td>18</td>
<td>NS</td>
</tr>
<tr>
<td>Inferior</td>
<td>10</td>
<td>11</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Disease activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2 attacks/day</td>
<td>11</td>
<td>1</td>
<td>2</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>&lt;2/day, ≥2/week</td>
<td>12</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>&lt;2 attacks/week</td>
<td>2</td>
<td>7</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Coronary arteriography</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No stenosis ≥ 70%</td>
<td>11</td>
<td>8</td>
<td>22</td>
<td>NS</td>
</tr>
<tr>
<td>1 vessel ≥ 70%</td>
<td>10</td>
<td>9</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>2-3 vessels ≥ 70%</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Spontaneous spasm</td>
<td>7 (28%)</td>
<td>3 (14%)</td>
<td>6 (17%)</td>
<td>NS</td>
</tr>
<tr>
<td>Abnormal ventriculogram</td>
<td>4 (16%)</td>
<td>7 (33%)</td>
<td>6 (17%)</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise test:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treadmill time (secs)</td>
<td>422 ± 193</td>
<td>441 ± 164</td>
<td>577 ± 147</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Maximal heart rate (beats/min)</td>
<td>130 ± 27</td>
<td>135 ± 26</td>
<td>145 ± 24</td>
<td>NS</td>
</tr>
<tr>
<td>Pressure-rate product (× 10⁻⁸)</td>
<td>23.8 ± 6.7</td>
<td>25.6 ± 6.3</td>
<td>27.8 ± 7.2</td>
<td>NS</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>10 (40%)</td>
<td>6 (29%)</td>
<td>5 (14%)</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>20.8 ± 15.5</td>
<td>21.4 ± 14.5</td>
<td>19.3 ± 13.4</td>
<td>NS</td>
</tr>
<tr>
<td>Myocardial infarction (deaths)</td>
<td>3 (2)</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Noncardiac deaths</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
mality, six of the 21 (29%) with ST depression and 10 of the 25 (40%) with ST elevation. Three patients had exercise-induced ventricular tachycardia, all of whom had ST elevation. In each case the tachycardia terminated spontaneously within 10 seconds of its onset. In no patient did systolic blood pressure decrease during exercise.

Follow-up

Patients were reevaluated at least every 3 months. The mean follow-up periods for the three groups are similar, approximately 20 months (table 3). In patients 17 and 22 (table 1), who had ST elevation, myocardial infarction occurred 1 month after the exercise test; both died suddenly at home within 2 months after infarction. Patient 3 (table 1, fig. 2), who had an infarction at 3 months, is alive 30 months later. None of the other 22 patients with exercise-induced ST elevation and none of the 21 patients with ST depression died or had a myocardial infarction during the follow-up period. Among the 36 patients with no ST abnormality during exercise, one patient with one-vessel disease had a myocardial infarction 2 weeks after the test, but has been asymptomatic during the subsequent 18 months and another, who was angina-free, died of a noncardiac cause (suicide) 4 months after the test.

Discussion

The results of this study suggest that in patients with variant angina, exercise testing will induce ST elevation in approximately one-third, isolated ST depression in approximately one-fourth and no ST-segment abnormality in slightly less than half the patients tested. The results of the exercise test cannot be predicted by most clinical measurements, including the extent or severity of fixed coronary stenoses. Coronary stenoses ≥ 70% were present in 56% of patients with ST elevation during exercise, in 62% of those with ST depression and in 39% of those with no ST abnormality, a difference that is not statistically significant.

The results of exercise testing were mentioned in three papers describing large series of variant angina patients. In the 20 cases reported by MacAlpin et al., exercise induced ST elevation in three, ST depression in three and no ST-segment shifts in 12; two patients were not tested. Maseri et al. performed a bicycle stress test on 96 of their 138 variant angina patients, monitoring three unspecified ECG leads. ST elevation occurred in 17, ST depression in 24 and pseudonormalization of negative T waves in 16; 29 patients had no diagnostic changes and the other 10 were not accounted for. The coronary arteriographic findings were not described for each type of ST-segment response. Twenty-one of 31 patients studied by de Servi et al. underwent a bicycle stress test, but neither the exact test protocol nor the ECG leads monitored were reported. Of seven patients with no fixed stenosis ≥ 50%, four had ST elevation and three had negative tests. Of 14 patients with coronary lesions, two tests showed ST elevation, six ST depression, four were negative and two were described as borderline.

The differences between studies in the prevalence of exercise-induced ST elevation can probably be attributed to differences in the degree of disease activity at the time of testing. In our study, ST elevation occurred during exercise in 11 of 14 patients who had an average of at least two spontaneous attacks of variant angina per day, but in only two of 31 who had an average of less than two attacks per week. This finding also may explain why ST elevation during exercise is reproducible in some cases but not in others; thus, all five of the retested patients with active variant angina had reproducible ST elevation and all three in an asymptomatic phase of their disease did not. Similarly, variant angina patients who become asymptomatic may not respond as they did during the active phase of their illness to other provocative tests, such as ergonovine administration.

Calcium-antagonist drugs reduce or eliminate spontaneous variant angina attacks and appear to be equally effective in blocking attacks induced by exercise. Diltiazem suppressed ST elevation during exercise in 11 of the 13 cases reported by Yasue et al. Our results are similar: Nifedipine, diltiazem or a combination of both completely blocked exercise-induced ST elevation in 10 of 12 cases.

In this study, a history of effort angina was equally common among patients with each of the three ST responses to exercise. Furthermore, effort angina was only slightly more common in patients with fixed lesions (26 of 41) than in those without (22 of 41). Likewise, effort angina occurred in four of nine patients without and 12 of 22 patients with fixed stenoses in the study of de Servi et al. and in seven of 30 patients (23%) without fixed lesions in Heupler's study.

Coronary artery spasm is accepted as the cause of ST elevation during exercise in variant angina. In variant angina patients with previous infarction (such as patient 22 in table 1), ST elevation may be caused by an akinetic segment and not by coronary spasm. ST depression during exercise in variant angina patients can be explained by three mechanisms. First, fixed coronary lesions could cause ST depression as in patients without variant angina. This explanation could account for 16 of the 21 patients in this study with exercise-induced ST depression, but not for the five who had no stenoses ≥ 50%. Spontaneous coronary spasm at rest can cause either ST elevation or depression, so one might postulate that exercise-induced spasm could also cause ST depression. Yasue et al. described four patients without variant angina who had exercise-induced ST depression caused by coronary spasm. In our study, coronary spasm could have caused the ST depression in two of the five patients without lesions ≥ 50%, because their thallium scans showed an exercise-induced defect; however, the three other patients had normal exercise thallium scans. The third potential cause of ST
depression in these patients, a false-positive response
similar to that found in other patient populations,
could be applied to the three remaining cases.

Does the ST-segment response to exercise have
prognostic importance in patients with variant angina?
Almost no data in the literature address this question.18 Lahiri et al.28 described five variant angina
patients with ST depression during exercise and ST
elevation in the recovery period. All had fixed coro-
nary lesions; three had a myocardial infarction within
8 weeks and two of the three died. In contrast, during
a mean follow-up period of 20 months in this study,
only five of 82 patients died or had a myocardial
infarction. Three of the five had ST elevation during
exercise and the other two had no ST abnormality.
Thus, although more patients or longer follow-up
might demonstrate that exercise-induced ST eleva-
tion carries a slightly worse prognosis than for the
other two groups, our results suggest at least that this
finding need not be considered an ominous prognostic
sign in variant angina. During the follow-up of this
study, almost all patients (77 of 82) received intensive
treatment with calcium-antagonist drugs. This may
account for the good prognosis for the entire group
and particularly for those with exercise-induced ST
elevation. Coronary spasm causes exercise-induced ST
elevation and is effectively blocked by calcium-
antagonist drugs; thus, it is not surprising that exer-
cise-induced ST elevation is of limited prognostic
value in treated patients.

The results of this study do not imply that an exer-
cise test is necessary to diagnose or treat patients with
variant angina. The test does not define a high-risk
subgroup and does not predict the underlying coro-
nary anatomy; in any case, coronary arteriography is
indicated in almost all variant angina patients to
detect the small minority with critical fixed lesions
that require urgent surgery. Exercise testing objec-
tively documents the effect of treatment with calcium-
antagonist drugs if ST elevation occurs before, but not
during, treatment; however, the clinical response to
such therapy may provide the equivalent data. Gaasch19
suggested that exercise testing might be useful if
patients with ST depression were more likely to
benefit from bypass surgery than others; however, ouresults suggest that for this subgroup, the short-term
prognosis without surgery is excellent.

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Figure 2. (A) Left coronary arteriogram (45° left anterior oblique, 25° craniocaudal angulation) of patient 3, a 47-year-old
man with active variant angina (table 1). A 40% proximal left anterior descending coronary artery stenosis is present. The right
coronary artery was normal. (B) Angina and ST elevation developed spontaneously during coronary arteriography. Repeat in-
jections at this time revealed severe coronary spasm at the site of the lesion. The coronary spasm resolved immediately after
nitroglycerin administration. (C) ECG during an episode of spontaneous rest angina, demonstrating ST elevation in leads
V3–V6. The ST segment returned to normal after nitroglycerin administration. (D) ECG during the tenth minute of an exercise
test at the onset of angina. The maximal heart rate was 169 beats/min. The ST segment, which was normal before exercise, is
elevated in leads 1, aV5, and V5–V6, and depressed in leads 2, 3 and aV4. The thallium scan revealed a large anteroseptal defect
not present on the control scan. (E) ECG 3 months later, 1 week after a prolonged episode of myocardial ischemic pain at rest.
Q waves have appeared in V1 and V2 and the T wave is inverted in V1–V4. (F) Left coronary arteriogram after myocardial infarc-
tion. The left anterior descending coronary artery is completely occluded at the site where coronary spasm had been demon-
strated. The left ventricular angiogram, which had been normal, reveals anterolateral and apical akinesis.


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