Significance of Exercise-induced ST-segment Elevation in Patients Without Myocardial Infarction

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SUMMARY Sixteen patients with exercise-induced ST-segment elevation and without a history of myocardial infarction or left ventricular aneurysm were studied. Fourteen complained of angina at rest, which was associated with ST-segment elevation in the same leads where it was recorded during exercise, and two patients had only exertional angina. Exercise-induced ST-segment elevation was generally reproducible in subsequent exercise tests performed in different hours of the day, but exercise tests repeated a mean of 15 months later did not induce this electrocardiographic abnormality. All patients had a marked susceptibility to coronary spasm, as shown by the response to the ergonovine test (12 positive tests in 12 patients) and by the occurrence of spontaneous spasm during coronary arteriography in two patients. In addition, coronary arteriography, performed in seven patients at the time of exercise-induced ST-segment elevation, revealed spasm of a major coronary vessel in all. In two patients we documented exercise-induced ST-segment elevation was accompanied by a decreased coronary blood flow and increased coronary vascular resistance. We conclude that exercise-induced ST-segment elevation in patients without a history of myocardial infarction or left ventricular aneurysm is caused by coronary spasm of a major coronary vessel.

ANGINA AT REST associated with ST-segment elevation is caused by a sudden reduction of myocardial oxygen supply because of severe coronary artery spasm, resulting in transmural ischemia. This pathogenetic mechanism has been clearly seen in patients with normal or near-normal coronary arteries and in those with significant organic lesions. Exercise-induced ST-segment elevation has been associated with the presence of left ventricular aneurysm, but its significance in patients without myocardial infarction is less clear. Most of the patients presenting with this phenomenon and without evidence of myocardial infarction or wall motion abnormalities have significant obstructions in proximal portions of large coronary vessels, suggesting that these obstructions could limit flow during exercise. However, in some patients with variant angina who show ST-segment elevation during or just after an exercise test, coronary spasm has been demonstrated by coronary arteriography performed at the time of this electrocardiographic abnormality. In some patients, the spasm was superimposed on a severe narrowing of the coronary vessels. McLaughlin et al. reported a patient with reproducible chest pain that occurred only in the immediate postexercise period associated with ST-segment elevation caused by spasm of a normal right coronary artery, arousing suspicion that a vasospastic mechanism could be operative even in patients without rest or nocturnal angina.

In this paper we describe 16 patients with exercise-induced ST-segment elevation without evidence of previous myocardial infarction or wall motion abnormalities. The purpose of our study was to assess the reproducibility, denied by some investigators, of exercise-induced ST-segment elevation, to prove the susceptibility of the patients with exercise-induced ST-segment elevation to coronary artery spasm; and to clarify the pathogenetic mechanism of exercise-induced ST-segment elevation by performing coronary arteriography or determining coronary blood flow at the time of this electrocardiographic abnormality.

Materials and Methods From January 1976 to December 1979, 2380 patients underwent exercise testing in our laboratory. Of these patients, 16 had ST-segment elevation ≥ 1 mm during or just after exercise testing and without evidence of myocardial infarction were included in this study. Myocardial infarction was excluded on the basis of the following criteria: absence of chest pain associated with serum enzyme elevations (creatine kinase, lactic dehydrogenase and glutamic oxaloacetic transaminase), absence of Q waves ≥ 40 msec in the ECG and no angiographic evidence of akinetic or dyskinetic areas of the left ventricle. The bicycle exercise was performed in the morning (8:30–11 a.m.) in the supine position with an initial work load of 50 W and subsequent increments of 25 W every 3 minutes. The exercise was stopped when angina, dyspnea, exhaustion or ST-segment elevation ≥ 2 mm occurred. A 12-lead ECG was taken before, at the end of exercise and at each minute during recovery. Leads V_4, V_5, V_6 were monitored during exercise and cuff blood pressure was measured at 3-minute intervals. To assess the reproducibility of the electrocardiographic changes, the exercise test was repeated once or more...
in different hours of the day in 14 patients. Drug therapy, including nitrates and nifedipine, was discontinued 12 hours before the study. No patient was receiving β-blocking agents or digitalis.

All patients underwent coronary arteriography using the method of Sones after premedication with 10 mg of diazepam. The left ventriculogram was performed in right anterior oblique projection before the arteriogram. When spontaneous anginal attacks occurred during the procedure, selective injections were repeated at the time of chest pain and after nitroglycerin administration. Significant coronary disease was thought to be present when there was an arteriographic narrowing greater than 50% of one or more arteries.

The exercise test was repeated in the same way as previously described during coronary arteriography in seven patients and the arteriogram was taken at the time of the electrocardiographic changes induced by exercise. Ergonovine maleate was administered intravenously in one patient during coronary arteriography and in 11 in the coronary care unit. The drug (0.05 mg/min) was administered intravenously and the injection stopped when ST-segment elevation ≥ 0.1 mV occurred or when the maximum dose of 0.4 mg had been reached.

In two patients we measured coronary blood flow using the thermodilution technique in basal conditions and during exercise in supine position with an initial work load of 25 W and subsequent increments of 25 W every 2 minutes. The catheter was introduced in the main coronary sinus and its position was frequently checked throughout the procedure. A physiologic saline solution at 24°C was injected for 20 seconds into the coronary sinus in basal conditions, every 2 minutes during exercise and at the time of exercise-induced ST-segment elevation, using a pump at a rate of 48 ml/min. Coronary blood flow was calculated using the formula

\[ V_1 (\frac{T_b - T_1}{T_b - T_m} - 1) \times 1.08 \]

where \( V_1 \) is the volume of injectate (ml/min), \( T_b, T_1 \) and \( T_m \) are the temperature of blood, injectate and mixture of blood and injectate, and 1.08 is a constant of the saline solution. Coronary vascular resistance was calculated by the quotient of mean arterial pressure (determined from the direct intra-arterial pressure) and coronary blood flow. Informed consent was obtained from each patient before the studies. The procedures did not cause any complications.

**Results**

**Clinical Features**

All the patients were male, with an average age of 47.8 years (range 38–56 years). Five patients complained of spontaneous angina, nine of spontaneous and exertional angina and two of only exertional angina. In nine patients angina was of recent onset (less than 3 months); in four, chest pain was most frequent during sleeping hours, especially in the early morning. In 13 patients an ECG was taken during a spontaneous attack of chest pain. In all, ST-segment elevation was recorded in the same leads where it had occurred during or after the exercise test.

**Exercise Test (table 1)**

ST-segment elevation occurred during exercise in eight patients, at the end of exercise in three patients and during the recovery period from 30 seconds to 3 minutes in five patients. Precordial leads were involved in eight patients, inferior or inferolateral leads in seven, and inferior and precordial leads in one patient. Exercise-induced ST-segment elevation was accompanied by severe chest pain in nine patients and mild chest discomfort in four, while three patients were completely asymptomatic. Three of the five patients showing ST-segment elevation during the recovery period had ST-segment depression during exercise in the same leads where ST-segment elevation occurred after exercise. During the test, seven patients developed premature ventricular complexes and one a slow ventricular tachycardia. Seven patients had conduction defects, four had a left anterior hemiblock and three had a left posterior hemiblock.

A second exercise test repeated in the morning in three patients gave the same results. Ten patients performed, on different days, a second exercise test in the morning and a third in the afternoon at 6:00 p.m. Seven patients had positive tests in the morning and in the afternoon, one patient had a positive test only in the morning, one patient only in the afternoon, and another patient had both tests negative. The negative tests were interrupted because of exhaustion in all patients. ST-segment elevation always occurred at the same time and work load of exercise in all except in two patients. In one patient one exercise test induced ST-segment elevation during exercise and another test induced ST-segment elevation during the recovery period. In the other patient, ST-segment elevation occurred during exercise, but at a different work load and double product (fig. 1).

**Angiographic Features**

In no patients were akinetic or dyskinetic areas of the left ventricle present. The average ejection fraction was 0.60 (range 0.48–0.83) and the average left ventricular end-diastolic pressure was 15 mm Hg (range 6–29 mm Hg). Coronary arteriography (table 2) showed normal or no significant coronary artery disease in four patients. Four patients had one-vessel disease, with involvement of the left anterior descending artery in two and of the right coronary artery in two. Five patients had two-vessel disease and three-three-vessel disease. One patient had a coronary artery spasm that completely occluded a normal right coronary artery during a spontaneous episode of chest pain, which was associated with ST-segment elevation in the inferior leads. Another patient had a complete spastic occlusion of the left anterior descending artery at the site of an organic 90% stenosis during a spon-
Table 1. Clinical and Electrocardiographic Data

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years), sex</th>
<th>Angina</th>
<th>ST elevation at rest</th>
<th>Exercise-induced ST elevation</th>
<th>Time of exercise-induced ST elevation</th>
<th>Ergonovine test</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51/M Spont</td>
<td>II, III, aVF</td>
<td>II, III, aVF</td>
<td>Stop</td>
<td>+* Nifedipine 40 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>44/M Spont, exert</td>
<td>V1-V3</td>
<td>V1-V3</td>
<td>Stop</td>
<td>+ CABG LAD, RCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>43/M Spont, exert</td>
<td>II, III, aVF</td>
<td>II, III, aVF</td>
<td>Stop</td>
<td>+ Nifedipine 80 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>46/M Spont</td>
<td>V1-V4</td>
<td>V1-V4</td>
<td>During</td>
<td>+ TNG ointment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>45/M Exert</td>
<td>II, III, aVF, V1-V6</td>
<td>II, III, aVF, V1-V6</td>
<td>During</td>
<td>+ CABG CFX, OMB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>45/M Spont, exert</td>
<td>II, III, aVF</td>
<td>II, III, aVF</td>
<td>Recovery</td>
<td>+ Verapamil 320 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>51/M Spont, exert</td>
<td>II, III, aVF, V1-V2</td>
<td>II, III, aVF, V1-V2</td>
<td>Recovery</td>
<td>+ CABG RCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>55/M Spont, exert</td>
<td>V1-V3</td>
<td>V1-V3</td>
<td>During</td>
<td>+ Nifedipine 40 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>44/M Spont</td>
<td>II, III, aVF, V4</td>
<td>II, III, aVF, V4</td>
<td>Recovery</td>
<td>Not done Nifedipine 80 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>43/M Spont, exert</td>
<td>V1-V4</td>
<td>V1-V4</td>
<td>During</td>
<td>Not done CABG LAD, Diag, RCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>56/M Spont</td>
<td>II, III, aVF, V1-V6</td>
<td>II, III, aVF, V1-V6</td>
<td>During</td>
<td>+ CABG LAD, Diag, OMB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>47/M Spont, exert</td>
<td>V1-V3</td>
<td>V1-V3</td>
<td>Recovery</td>
<td>+ CABG LAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>52/M Exert</td>
<td>—</td>
<td>V1-V3</td>
<td>During</td>
<td>Not done CABG LAD, OMB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>54/M Spont, exert</td>
<td>—</td>
<td>V1-V3</td>
<td>During</td>
<td>+ CABG LAD, Diag</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>51/M Spont, exert</td>
<td>V1-V4</td>
<td>V1-V4</td>
<td>During</td>
<td>Not done CABG LAD, Diag, CFX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>38/M Spont</td>
<td>II, III, aVF</td>
<td>II, II, aVF</td>
<td>Recovery</td>
<td>+ Nifedipine 80 mg/day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Test performed during coronary arteriography.

Abbreviations: Spont = spontaneous angina; Exert = exertional angina; Stop = at the end of exercise; + = positive; CABG = coronary artery bypass graft; LAD = left anterior descending artery; RCA = right coronary artery; Diag = first diagonal branch; CFX = circumflex artery; OMB = obtuse marginal branch; TNG = 25% nitroglycerin ointment, 2 inches every 6 hours.

Figure 1. Case 16. Two exercise tests performed in different hours of the day induce ST-segment elevation in the same leads at different rate-pressure products.

Ergonovine Test

An ergonovine maleate test, performed during coronary arteriography in case 1, elicited a positive spontaneous attack associated with ST elevation in anterior leads. In both patients, sublingual nitroglycerin promptly relieved the pain and reversed the spasm.
response by inducing chest pain associated with ST-segment elevation and complete spastic occlusion of the proximal portion of the right coronary artery at the site of a 30% organic stenosis. Ergonovine testing, performed in 11 patients in the coronary care unit (table 7), induced ST-segment elevation in all 11 in the same leads where it was recorded during exercise-induced attacks.

Exercise Test During Coronary Arteriography

Chest pain and ST-segment elevation developed in all seven patients during or just after the exercise test. Three of these patients (cases 3, 4 and 6) have been reported previously. Coronary arteriograms performed at the time of ST-segment elevation showed spasm of the left anterior descending artery in four cases and of the right coronary artery in three cases (table 2). The electrocardiographic site of ST-segment elevation corresponded to the area supplied by the artery in which coronary artery spasm occurred. The spasm was superimposed on significant coronary stenosis of the left anterior descending artery in four cases (fig. 2) and of the right coronary artery in one; in two the spasm occluded a right coronary artery with nonsignificant obstructive lesions. In four patients, angina and the electrocardiographic changes subsided within 1–3 minutes after 0.4 mg of sublingual nitroglycerin. In three patients immediate relief was obtained by intracoronary administration of 0.35 mg of nitroglycerin (fig. 3).

Coronary Blood Flow During Exercise (table 3)

In both patients studied, coronary blood flow rose and coronary vascular resistance declined during exercise before the appearance of ST-segment elevation. When ST-segment elevation developed, coronary blood flow abruptly decreased, with an increase in coronary vascular resistance (fig. 4).

<table>
<thead>
<tr>
<th>Case</th>
<th>Spontaneous spasm</th>
<th>Exercise-induced spasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100% LAD</td>
<td>90% RCA</td>
</tr>
<tr>
<td>2</td>
<td>100% LAD</td>
<td>99% LAD</td>
</tr>
<tr>
<td>3</td>
<td>90% RCA</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>90% RCA</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>90% RCA</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>90% RCA</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>99% LAD</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>100% RCA</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>100% LAD</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>100% LAD</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>100% OM</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>90% RCA</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>90% RCA</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>90% LAD</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>90% LAD</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>90% LAD</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: LAD = left anterior descending artery; RCA = right coronary artery; CFX = circumflex artery; Diag = diagonal branch; OM = obtuse marginal branch.

<table>
<thead>
<tr>
<th>Case</th>
<th>CBF (ml/min)</th>
<th>CVR (mm Hg/ml/min)</th>
<th>25 W at 2 minutes</th>
<th>50 W at 2 minutes</th>
<th>75 W at 2 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>14*</td>
<td>112</td>
<td>0.87</td>
<td>183</td>
<td>0.64</td>
<td>232</td>
</tr>
<tr>
<td>15†</td>
<td>140</td>
<td>0.89</td>
<td>253</td>
<td>0.61</td>
<td>170</td>
</tr>
</tbody>
</table>

*Exercise test interrupted at a work load of 75 W at 2 minutes because of chest pain and ST-segment elevation in leads V<sub>1</sub>–V<sub>3</sub>

*Exercise test interrupted at a work load of 50 W at 2 minutes because of chest pain and ST-segment elevation in leads V<sub>1</sub>–V<sub>4</sub>.

Abbreviations: CBF = coronary blood flow; CVR = coronary vascular resistance.
Clinical Course

Nine patients underwent coronary bypass surgery, and one died perioperatively. The other eight patients were angina-free after a mean period of 12.5 months (range 3–37 months). Medical treatment with calcium antagonists (nifedipine 10–20 mg every 6 hours or verapamil 80 mg every 6 hours) was started in six patients with complete relief of angina in five and improvement in one after a mean follow-up period of 18 months (range 2–44 months). One patient treated with nitroglycerin ointment (2 inches every 6 hours) died suddenly 2 months after discharge.

Exercise tests repeated in 11 patients (seven surgically treated and four medically treated) after a mean period of 15 months (range 3–37 months) were negative in all but two medically treated patients who had chest pain associated with ST-segment depression.

Discussion

Our data indicate that in patients without myocardial infarction and without left ventricular aneurysm, exercise-induced ST-segment elevation is caused by spasm occluding a large coronary vessel. In fact, in all seven of the patients in whom coronary arteriography was performed at the time of this electrocardiographic abnormality, we demonstrated either complete or subtotal spastic obstruction of a major coronary branch. In two patients we documented that exercise-induced ST-segment elevation was accompanied by a decline of coronary blood flow and an increase in coronary vascular resistance. Most of our patients also complained of angina at rest, associated with ST-segment elevation in the same leads in which it was recorded during exercise and showed a marked susceptibility to coronary spasm as suggested by the response to the ergonovine test (12 positive tests in 12 patients studied) and by the occurrence of spontaneous spasm during coronary arteriography in two patients. Exercise-induced ST-segment elevation is generally reproducible in different exercise tests, even in different hours of the day. Therefore, in contrast with the data of Yasue et al.,17 we found no circadian variation of exercise capacity in our patients. Exercise testing repeated a mean of 15 months later was negative in all except in two patients who had pain associated with ST-segment depression. The repeated exercise tests did not induce ST-segment elevation. We do not know whether this fact was secondary to the good result of surgical and medical treatment or was the natural course of the disease.

Exercise-induced ST-segment Elevation and Severe Coronary Artery Disease

Exercise-induced ST-segment elevation has been reported to occur in patients with severe coronary artery disease. Fortuin and Friesinger13 studied 12 patients with this electrocardiographic abnormality, which was produced by the exercise test. Because 11 patients had severe coronary artery disease, they concluded that a causal relationship was present between the arteriographic lesions and the exercise-induced electrocardiographic changes. Longhurst and Kraus14 reported similar conclusions in a recent study of 46 patients with exercise-induced ST elevation and no evidence of myocardial infarction. In that study, when ST-segment elevation occurred in anterior leads a left anterior descending artery obstruction was evident in 86% of cases, but inferior ST elevation did not correlate with coronary artery disease. Coronary arteriography was not performed during exercise in those patients, so we cannot rule out that coronary spasm caused exercise-induced ST elevation.

In our study a vasospastic mechanism for exercise-induced ST elevation was demonstrated in patients...
with nonsignificant coronary artery disease and in patients with severe coronary organic lesions. We have documented spasm superimposed on an organic stenosis of the left anterior descending artery in four patients and of the right coronary artery in one patient at the time of this electrocardiographic abnormality. Thus, a vasospastic mechanism may be involved even when a coronary obstructive disease is present.

Mechanism of Spasm during Exercise: Role of Alpha-adrenergic Stimulation

Early experimental studies have demonstrated that the primary determinant of coronary blood flow is myocardial oxygen consumption. Therefore, the effects of exercise on the coronary tree should be a reflection of an increase of myocardial metabolic demands. However more recent investigations have pointed out the importance of autonomic innervation in determining coronary blood flow even in presence of vasodilating metabolites and a substantial body of evidence suggests that alpha-adrenergic mediated vasoconstriction may cause chest pain and electrocardiographic changes in some patients with coronary artery disease. Yasue et al. induced anginal attacks associated with ST-segment elevation by the administration of the alpha-stimulating agent epinephrine. Mudge and co-workers demonstrated an increase of coronary vascular resistance during cold pressor test, a stimulus known to induce vasoconstriction mediated through activation of alpha-adrenergic receptors. Furthermore, a transient prolongation of the corrected QT interval analogous to that described with unilateral or asymmetric stellate ganglion stimulation has been found just before spontaneous or ergonovine-provoked coronary spasm. Alpha-blocking agents have been shown to be effective in reversing and preventing vasospastic anginal attacks. These data support the hypothesis that altered adrenergic activity could be the mechanism whereby temporarily increased tonus of the coronary arteries occurs in patients with vasospastic angina.

Experimental data have shown that during exercise alpha blockade induces a more marked decline of coronary vascular resistance than that occurring in absence of such blockade, suggesting that alpha-adrenergic vasoconstriction occurs during physical activity. Sympathetic tone increases during exercise and alpha-adrenergic activation can result in coronary spasm, so exercise-induced neurogenic stimulation could trigger coronary spasm in susceptible patients.

Implications

Recognition of the cause underlying the electrocardiographic changes occurring during exercise is ex-
tremely important for a rational approach to the management of patients with ischemic heart disease. Propranolol should be the most effective treatment if exertional angina is secondary to an increase of myocardial metabolic demands, but it could be ineffective and even detrimental if a vasospastic mechanism is implicated. In such cases, calcium antagonists like nifedipine\(^{33-37}\) and verapamil\(^{38}\) should be the drugs of choice. In addition, \(\alpha\)-adrenergic blockade with phentolamine and phenoxybenzamine may be beneficial in both spontaneous and exertional angina by preventing \(\alpha\)-adrenergically mediated vasoconstriction. The efficacy of coronary bypass grafting in patients with vasospastic angina is still controversial.\(^33,\)\(^34,\)\(^47,\)\(^48\) Long-term results have been satisfactory, with improvement to an asymptomatic state in most of our patients, suggesting that the surgical approach can be effective in relieving angina when spasm is superimposed on a significant fixed coronary lesion. However, more patients must be studied before a definite conclusion can be reached about the role of surgery, and further studies are required to clarify the mechanism by which coronary bypass grafting can be effective in such patients.

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