Coronary Artery Spasm During Exercise: Treatment with Verapamil

Ben Freedman, M.B., Richard F. Dunn, M.B., David R. Richmond, M.B., and David T. Kelly, M.B.

Summary

Six patients who had documented coronary spasm and no coronary artery with organic obstruction > 50% developed angina and ST-segment elevation on exercise testing. Oral verapamil, 160–480 mg/day, prevented exercise-induced ischemia in all patients and increased maximal work capacity from 611 ± 250 kpm to 808 ± 160 kpm (p < 0.02). In two patients, a relationship between the prevention of exercise-provoked ischemia and the plasma concentration of verapamil was demonstrated, and in one of these, the relationship had a diurnal pattern. Patients with variant angina may develop coronary spasm on effort and often respond to verapamil.

Exercise-induced Angina

Exercise-induced angina is usually caused by an imbalance between increased myocardial oxygen demand and blood supply to the myocardium because of fixed atheromatous coronary artery obstruction. Rarely, exertional angina may result from a transient decrease in coronary blood flow due to an increase in coronary vasomotor tone, producing spasm.1–4 Verapamil is effective in preventing spontaneous attacks of angina at rest in patients with coronary artery spasm.5 In this report we present six patients with chest pain on exercise thought to be produced by coronary artery spasm. Verapamil prevented both chest pain and ST-segment elevation on effort. Two patients demonstrated a dose-response relationship.

Materials and Methods

Patient Selection

Six patients with chest pain and ST-segment elevation on exercise, but without significant organic coronary obstruction (> 50% luminal diameter reduction) at coronary arteriography, were selected for study. All patients had been referred for diagnostic cardiac catheterization because of recurrent chest pain present for an average of 23 months (range 2–108 months). Five men and one woman were studied; mean age 56 years (range 49–64 years). All had experienced chest pain on exertion, but the predominant symptom was angina at rest. Five had recurrent nocturnal chest pain that awoke them from sleep. At presentation, five of the patients were taking β-blocking drugs, which had not reduced the frequency or severity of symptoms. The resting ECG was normal in five and showed left ventricular hypertrophy with ST-T-wave changes in one. No patient had a history of myocardial infarction.

Coronary Arteriography and Ergonovine Testing

Selective coronary arteriography was performed using either the Judkins or Sones technique. Left and right anterior oblique and angulated views were routinely obtained and the films were reviewed independently by two experienced angiographers. No patient showed obstruction of more than 50% in any coronary artery, but all showed 20–50% obstruction in one or more arteries. Coronary artery spasm was confirmed by ergonovine provocation in all patients, using incremental doses from 0.05 mg to 0.3 mg, as previously described.6 In two patients, ergonovine was given during angiography and spasm was visualized by repeat coronary injection.7 The four other patients were given ergonovine after angiography and the resulting ischemia was inferred by transient ST-seg-
Table 1. Angiographic Findings and Ergonovine Test Results

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Coronary angiography</th>
<th>Left vent.</th>
<th>Cor. angio. % narrowing</th>
<th>ECG ST changes (mm)</th>
<th>Pain</th>
<th>T1-201</th>
<th>ECG during spontaneous angina ST changes (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EW</td>
<td>53</td>
<td>M</td>
<td>RCA 20% LCX 20%</td>
<td>Normal</td>
<td>RCA 100% LAD slow*</td>
<td>ST↑ 2, 3, F (10 mm)</td>
<td>+</td>
<td></td>
<td>Not observed</td>
</tr>
<tr>
<td>EK</td>
<td>55</td>
<td>F</td>
<td>LAD 50%</td>
<td>Normal</td>
<td></td>
<td>ST↑ V1, V6 (4 mm)</td>
<td></td>
<td></td>
<td>ST↑ V1 (1 mm)</td>
</tr>
<tr>
<td>MG</td>
<td>46</td>
<td>M</td>
<td>LAD 30% RCA 40% LCX irreg.</td>
<td>Mild ant. hypo-kinesis</td>
<td>ST↑ V1-4 (3 mm)</td>
<td>+</td>
<td></td>
<td>ST↑ V1, V6 (½ mm)</td>
<td></td>
</tr>
<tr>
<td>WC</td>
<td>49</td>
<td>M</td>
<td>LAD 30% RCA 30% LCX 30% irreg.</td>
<td>Normal</td>
<td>ST↑ V1-4, L (18 mm) ST↑ 2, 3, F (1 mm)</td>
<td>+</td>
<td></td>
<td>ST↑ V1-5 (5 mm)</td>
<td></td>
</tr>
<tr>
<td>AH</td>
<td>52</td>
<td>M</td>
<td>RCA 40%</td>
<td>Normal</td>
<td>ST↑ 2 (2 mm)</td>
<td>+</td>
<td></td>
<td>ST↑ 2, 3, F (6 mm) VT</td>
<td></td>
</tr>
<tr>
<td>VG</td>
<td>62</td>
<td>M</td>
<td>LAD 40% LCX 50%† RCA irreg.</td>
<td>Normal</td>
<td>ST↑ V1-4 (4 mm)</td>
<td>+</td>
<td></td>
<td>ST↑ V1-6, L (5 mm)</td>
<td></td>
</tr>
</tbody>
</table>

*LAD not injected during angina. After relief of RCA spasm, LAD flow was slow and confined to diastole. Precordial leads were not recorded during spasm.
†LCX = small aberrant artery arising from right coronary cusp.

Abbreviations: RCA = right coronary artery; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; irreg = minor irregularities; RD = reversible thallium-201 defects; ST↑ = ST-segment elevation; ST↓ = ST-segment depression; + = pain provoked; VT = ventricular tachycardia; ant. = anterior; vent. = ventriculography; 1, 2, 3 = lead 1, 2, 3; L = aV_L; F = aV_F.

Ergonovine test elevation on a 12-lead ECG and a reversible defect on thallium-201 myocardial scintigraphy. The details of angiography and ergonovine testing are shown in table 1.

Exercise Testing

Exercise tests were performed using a graded, continuous, multistage protocol on a bicycle ergometer. Patients exercised for 2 minutes at each work level, with increments of 150 kpm for males and 100 kpm for females, until symptoms of chest pain or fatigue stopped the test. Blood pressure was recorded every 2 minutes during exercise. The ECG was continuously monitored during exercise and a 12-lead ECG was recorded every minute during and after exercise. The ECG was considered positive if there was ≥ 1 mm of horizontal or upsloping ST-segment elevation for 0.08 second in three consecutive beats or ≥ 1 mm of horizontal or downsloping ST-segment depression for 0.08 second in three consecutive beats.

In patient EK, a supine straight-leg raising exercise was performed both before and during coronary angiography, and in patient EW, a treadmill exercise test had been performed at another center before referral.

Baseline Exercise Test

A baseline exercise test was performed in five patients who had not received cardiac therapy for at least 24 hours. The sixth patient, MG, who had hypertension, was maintained on metoprolol, digoxin and a diuretic for both baseline and verapamil exercise tests.

Five of the patients were exercised more than once. Thallium myocardial perfusion scans were performed during the baseline exercise tests in four of the patients, as previously described. The unprocessed scintigraphic photos were read by three experienced observers without knowledge of the clinical details. A consensus of the observers was taken for the presence and site of defects. The interobserver variability for this technique was 7%.

Verapamil Exercise Test

All patients required verapamil, 160–480 mg/day, to prevent angina. The exercise test was repeated after at least 4 days of verapamil therapy. Patient MG had resting ECG changes due to hypertension and digitalis effect, so the thallium scan was repeated during the verapamil exercise test in this patient. In patients VG and AH, venous blood samples were withdrawn at the end of exercise tests on different verapamil dose schedules to assay verapamil plasma levels.

Verapamil Plasma level

Verapamil levels in plasma were measured using a high-pressure liquid chromatography method described by Harapat and Kates.

Statistical Analysis

Data were analyzed by the t test for paired data.

Results

The results of the exercise stress tests are summarized in table 2. Baseline exercise tests provoked
angina and ST-segment elevation during exercise in all patients. Repeat baseline exercise testing performed in five of the patients produced angina and ST-segment elevation, indicating ischemia was reproducible when the patients were not taking verapamil. In all patients, the ECG changes during exercise testing occurred in the same leads as in spontaneous or ergonovine-induced angina. Four patients underwent exercise thallium scanning and all had defects reversible at 4 hours. In two, EK and MG, the defects were in the left anterior descending (LAD) distribution and corresponded to the site of ST elevation produced by both exercise and ergonovine testing. In the other two, WC and EW, the reversible defects were apical and were associated with anterior and both anterior and inferior ST elevation, respectively. In patient EW, who had simultaneous ST elevation in two areas, injection of ergonovine during coronary angiography provoked right coronary artery (RCA) spasm, but the left coronary artery was not injected at the time, nor was a 12-lead ECG taken. When the RCA spasm was relieved by nitroglycerin, flow in the LAD was slow and limited to diastole, which suggested that LAD as well as RCA spasm may have occurred.

Patient EK performed supine straight-leg raising exercise during cardiac catheterization and developed angina during exercise, as had occurred during similar exercise on the previous day, when there were associated ST-segment changes (table 2). Ergonovine was injected into the LAD immediately after exercise and revealed a 95% obstruction at the site of a previously observed 50% organic lesion, which remained after nitroglycerin administration (fig. 1). In this patient, coronary artery spasm caused myocardial ischemia immediately after exercise. We felt that spasm had occurred during exercise, although for technical reasons the artery was injected only after exercise.

All patients underwent repeat exercise testing while on oral verapamil therapy (table 2). Verapamil prevented angina in all six patients at higher levels of work, and ST-segment changes no longer occurred in

Table 2. Results of Exercise Tests

<table>
<thead>
<tr>
<th>Pt</th>
<th>Date</th>
<th>Time (hours)</th>
<th>Medication</th>
<th>W_max (kpm)</th>
<th>Max HR (beats/min)</th>
<th>Max SBP (mm Hg)</th>
<th>Angina</th>
<th>Max Δ ST</th>
<th>Thallium-201 scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>EW29/12/78</td>
<td>1230</td>
<td>Atenolol 100 mg bd</td>
<td>TM</td>
<td>110</td>
<td>+</td>
<td>ST: 2, 3, F (7 mm)</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ST: 1, L, V4-6 (2 mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ST: V1,4 (4 mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24/1/79</td>
<td>0900</td>
<td>Nil</td>
<td>600</td>
<td>111</td>
<td>115</td>
<td>+</td>
<td>ST: 2, 3, F (3 mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27/4/79</td>
<td>1000</td>
<td>V 40 mg qid</td>
<td>1000</td>
<td>150</td>
<td>200</td>
<td>No changes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EK20/2/79</td>
<td>1000</td>
<td>Nil</td>
<td>400</td>
<td>142</td>
<td>150</td>
<td>+</td>
<td>ST: V1 (1.5 mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26/2/79</td>
<td>0900</td>
<td>V 80 mg qid</td>
<td>550</td>
<td>146</td>
<td>125</td>
<td>No changes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22/3/79</td>
<td>0900</td>
<td>Nil</td>
<td>SLR-9'</td>
<td>118</td>
<td>+</td>
<td>ST: V1 (1.5 mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23/3/79</td>
<td>0900</td>
<td>Nil</td>
<td>SLR-6'</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>RD anteroseptal apex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MG7/6/78</td>
<td>1100</td>
<td>*M</td>
<td>450</td>
<td>107</td>
<td>195</td>
<td>+</td>
<td>ST: V1 (2 mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9/5/79</td>
<td>1000</td>
<td>*M + V 80 mg qid</td>
<td>750</td>
<td>120</td>
<td>230</td>
<td>−</td>
<td>ST: L (1 mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WC5/7/79</td>
<td>0900</td>
<td>Nil</td>
<td>950</td>
<td>159</td>
<td>220</td>
<td>+</td>
<td>ST: V1, L (1 mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/7/79</td>
<td>1100</td>
<td>Nil</td>
<td>900</td>
<td>160</td>
<td>210</td>
<td>+</td>
<td>ST: V1,2 (1 mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/7/79</td>
<td>1000</td>
<td>V 160 mg tds</td>
<td>900</td>
<td>134</td>
<td>230</td>
<td>−</td>
<td>No changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AH12/10/79</td>
<td>0900</td>
<td>Nil</td>
<td>700</td>
<td>134</td>
<td>170</td>
<td>+</td>
<td>ST: 2, 3, F, V6 (2 mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12/10/79</td>
<td>1130</td>
<td>Nil</td>
<td>800</td>
<td>148</td>
<td>190</td>
<td>+</td>
<td>ST: 2, 3, F (3 mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16/10/79</td>
<td>1030</td>
<td>V 80 mg tds + (128) 3 hrs after dose</td>
<td>900</td>
<td>150</td>
<td>220</td>
<td>−</td>
<td>No changes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
five. The ECGs of baseline and verapamil exercise tests in patient VG are shown in figure 2. In patient MG, who was taking digitalis, resting ST-T changes prevented interpretation of the baseline exercise ECG; the exercise thallium scan showed reversible anteroseptal and apical defects. During the exercise test on verapamil, he had no associated angina, and the thallium scan at peak exercise was normal.

The verapamil exercise tests were performed 4–8 days after the baseline tests in four patients, and 3 and 11 months after the baseline tests in two patients. The verapamil exercise tests were performed at the same time of day as the baseline tests except in patient VG, who developed exercise-induced ischemia in both the morning and the afternoon.

The mean maximum work load achieved during the baseline exercise tests was 611 ± 250 kpm (mean ± SD) and 808 ± 160 kpm during the exercise tests on verapamil (p < 0.02). The mean maximum heart rate during baseline exercise tests was 129 ± 23 beats/min, and on verapamil it was 141 ± 12 beats/min (NS). The mean maximum systolic blood pressure during the baseline exercise tests was 168 ± 38 mm Hg, while on verapamil it was 194 ± 43 mm Hg (NS). The mean rate-pressure product at maximum work loads during the baseline tests was 223 ± 75 × 10², and at the same work loads during the verapamil tests it was 229 ± 67 × 10² (NS).

In patients VG and AH, the verapamil plasma levels were measured and related to the exercise response. Figure 3 shows the relationship between plasma verapamil concentration, the magnitude of ST-segment elevation, and the maximum exercise level achieved in patient VG. Moderately severe angina, accompanied by 5 and 4.5 mm of ST-segment elevation (V₁₋₄) at low work levels, occurred during the two baseline tests. At the lowest plasma level of verapamil (17 ng/ml), moderately severe angina was still experienced at a low work load, but less ST elevation (2.5 mm) was recorded. At a higher plasma level (25 ng/ml), he achieved a greater work load with slight angina and only 1.5 mm of ST elevation. At the highest plasma level (209 ng/ml), 1.5 hours after 160 mg of verapamil, no angina or ST elevation occurred at this patient’s maximum work load (fig. 2). The relationship between verapamil plasma concentration and response for AH is shown in figure 4. Plasma levels > 100 ng/ml consistently prevented ischemic changes
during exercise. There appeared to be a variable response to verapamil therapy that was caused by diurnal variation in exercise-induced ischemia. Exercise performed in the morning shifted the dose-response curve to the right compared with exercise performed in the afternoon. Verapamil plasma levels sufficient to prevent angina and ST-segment elevation in the afternoon did not prevent angina or ST-segment elevation in the morning.

Discussion

Angina of effort usually occurs when coronary blood flow through a narrowed artery cannot increase enough to meet the increased myocardial oxygen demand. None of our patients had severe (>50%) atheromatous obstruction at coronary angiography, and myocardial ischemia was thought to be due to a transient decrease in coronary blood flow during exercise. In patient EK, we observed reversible coronary vasospasm directly at arteriography after exercise, and we inferred it in the five other patients from chest pain, ST-segment elevation on the ECG or thallium
defects during exercise. Five of our six patients complained of recurrent nocturnal chest pain, a feature of variant angina caused by coronary spasm, and in all six the ergonovine test was positive. Ischemia during exercise has occurred in 25% of our series of 28 patients with variant angina and nonsignificant coronary lesions. Others have also reported patients with variant angina who developed angina of effort. When no severe atheromatous obstruction was found, coronary artery spasm was postulated and then demonstrated by angiography during exercise.

Calcium-antagonist vasodilators are effective in preventing recurrent chest pain in patients with variant angina and insignificant organic coronary atherosclerosis. In all of our patients, verapamil prevented ischemia on repeat exercise testing at higher work levels. In five of the six patients, spontaneous attacks were completely suppressed and the sixth had a modest reduction in frequency of spontaneous angina. Prevention of exercise-induced ischemia may be a useful predictor of the response of spontaneous episodes to therapy. Previous reports have also shown a beneficial response with other calcium-antagonist drugs. These drugs produce coronary vasodilatation and prevent vasospasm by blocking calcium influx to coronary vascular smooth muscle. The effects of the calcium antagonists on heart rate and blood pressure are not important in preventing exercise-induced angina in this group of patients because ischemia results from a decrease in coronary blood flow and not from an excessive myocardial oxygen demand. This contrasts with the mechanism of exercise ischemia in patients with fixed coronary obstruction, for which the therapeutic effect of the β-adrenergic blocking drugs is well established. In our patients, the heart rate and blood pressure responses to exercise increased on verapamil compared with baseline. The difference was not significant and may have been due to verapamil preventing spasm and allowing the patients to exercise longer.

Because attacks of chest pain in patients with variant angina may vary spontaneously with time, the baseline exercise tests were repeated in four patients, and angina was produced at similar work levels. The exercise test on verapamil was also performed within 8 days of the baseline test in four of the patients. In patients EW and MG, the exercise test on verapamil was performed at 3 and 11 months, respectively, after the baseline test, and may have contributed to the negative test on verapamil. This was an open study of verapamil therapy without placebo control and therefore places a limitation on the precise assessment of therapy. However, a placebo effect could be excluded in patients AH and VG, as positive
tests occurred while the patients were taking verapamil when the plasma concentration was low, but not when the concentration was high. Training effects may also have contributed to our findings, as the sequence of baseline and verapamil exercise tests was not randomized, although this is unlikely, as in patients EK and AH, a negative test on verapamil occurred between two positive tests off verapamil. In three patients, exercise tests were repeated on the same day, at a mean of 2 1/2 hours after the previous test. Thadani et al.9 showed that left ventricular pressures are lower on repeat exercise testing at 25 minutes in patients with significant coronary lesions. This effect was not important in our group of patients as the repeat exercise test was positive in all three when not on therapy.

The site of ECG changes and thallium defects suggests that the same artery was involved in exercise-induced, ergonovine-provoked and spontaneous angina. The similarity between the site of spontaneous and ergonovine-induced ischemia has been noted.6, 21 In patient EW, the first baseline exercise test revealed inferior ST-segment elevation, but the second test showed anterior ST-segment elevation as well. While RCA spasm seen during ergonovine administration would explain inferior ST-segment elevation, anterior ST-segment elevation implies additional LAD spasm. The unusual angiographic flow pattern during the LAD injection after relief of RCA spasm in this patient supports the possibility of additional LAD spasm. We have seen simultaneous RCA and LAD spasm in a patient during ergonovine provocation,6 and in another patient, we observed spontaneous RCA or LAD spasm on separate occasions.22

Few studies have been reported on the pharmacokinetic and pharmacodynamic properties of verapamil because it is difficult to measure drug levels in plasma.23, 24 A dose-response relationship was demonstrated for atrioventricular nodal conduction and left ventricular function in the dog by means of a fluorimetric assay,25 but this technique cannot differentiate metabolites from unchanged verapamil. The chromatographic technique we used separates verapamil from its metabolites and measures both simultaneously.16, 11 In the present study a relationship was demonstrated in two patients between the suppression of ischemia provoked by exercise and the plasma level of unchanged verapamil. Although these observations are preliminary, they indicate a relationship between the plasma level and the clinical relief of symptoms. A diurnal variation appears to exist in some patients with exercise-induced coronary artery spasm. Yasue et al.3 showed that angina and ST-segment elevation provoked by exercise in the early morning did not occur at the same level of exercise in the afternoon. We did not routinely study this diurnal variation, but the three patients exercised both in the morning and afternoon developed angina and ST elevation with similar levels of work at either time of day. A diurnal pattern of exercise response could not account for the beneficial effects of verapamil in our patients, as in five the verapamil test was performed at the same time of day as the baseline test, and in the sixth, patient VG, exercise-induced ischemia occurred in both the morning and the afternoon, with positive baseline tests occurring in the afternoon. Patient AH (fig. 4) demonstrated a diurnal dose-response relationship and required less verapamil to prevent angina in the afternoon than in the morning.

Beta-adrenergic blocking drugs are effective in patients with exercise-induced angina from severe atheromatous coronary obstruction, but are thought to be ineffective in patients with variant angina due to coronary artery spasm13 and may even aggravate attacks.17, 26, 27 Yasue et al.2 found that propranolol did not relieve exercise-induced spasm in their patients. Five of our six patients were taking β-adrenergic blocking drugs before study without relief of or decrease in their attacks of pain. This emphasizes that when exercise-induced coronary spasm is suspected, treatment with calcium-antagonist vasodilators is preferable to β blockade and is effective.

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