Short- and long-term efficacy of high-dose oral diltiazem for angina due to coronary artery disease: a placebo-controlled, randomized, double-blind crossover study

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ABSTRACT The effects of oral diltiazem (360 mg/day) on exercise tolerance, left ventricular performance, and plasma lactate and catecholamine levels were studied in 13 patients with atherosclerotic coronary artery disease in a placebo-controlled, randomized, double-blind protocol. Exercise duration to the onset of ischemic ST segment depression, time to angina pectoris, and time to peak exercise improved by 120, 174, and 144 sec, respectively (p < .0001). Left ventricular ejection fraction, as determined by radionuclide angiography, increased in patients at rest from 52 ± 11% (mean ± SD) during placebo therapy to 58 ± 11% during diltiazem therapy (p < .001); at peak exercise ejection fraction increased from 44 ± 11% during placebo treatment to 52 ± 15% during diltiazem therapy (p < .01). The mean plasma norepinephrine level in patients at rest increased from 498 ± 221 pg/ml during placebo treatment to 667 ± 272 pg/ml during diltiazem therapy (p < .05). Resting standing blood pressure and supine and standing diastolic blood pressures decreased significantly with diltiazem. In all 10 patients followed over a long term, oral diltiazem caused persistent improvement in exercise performance at 12 to 20 weeks, without evidence of placebo effects. Thus, diltiazem is highly effective in divided doses of 360 mg/day for the therapy of chronic angina pectoris due to coronary artery disease.

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DILTIAZEM HYDROCHLORIDE has been shown to be effective in the treatment of exertional angina pectoris in doses of 240 mg/day.1 Although divided doses of up to 360 mg/day have been useful in treating patients with variant angina,2,3 previously reported studies have not evaluated this dose for the long-term therapy of patients with exertional angina pectoris. Dose titration studies have shown that beneficial effects of diltiazem can be demonstrated by exercise treadmill testing in patients with coronary artery disease at doses of 240 mg/day, but not at lower doses.4-7 Single doses of 90 to 120 mg have also been demonstrated to be effective.8,9 Little data exist concerning the effects of higher doses of diltiazem (360 mg/day) on resting hemodynamics and left ventricular performance during exercise. Therefore, the purpose of this study was to evaluate the safety, efficacy, and hemodynamic effects of 360 mg/day diltiazem in divided doses for the treatment of chronic stable exertional angina pectoris.

Materials and methods

Patient selection. Thirteen patients between the ages of 49 and 70 years (mean 61.5) were included in the study group. Study patients were required to have had stable angina pectoris for at least 3 months, to have typical exertional chest pain relieved by nitroglycerin, and to have previous exercise treadmill test results positive for both chest pain and ischemic ST segment depression in an anterolateral precordial lead. Patients who had had a myocardial infarction in the preceding 6 months or had concurrent congestive heart failure, valvular heart disease, significant arrhythmias, or hypertension were excluded. Of the 13 patients who participated, 11 had previously documented myocardial infarctions. Of the 10 patients undergoing
coronary arteriography, six had significant (>70% diameter narrowing) three-vessel disease, one had two-vessel disease, and three had one-vessel disease. Patients provided informed consent on a form approved by the Institutional Review Board of the University of Texas Health Science Center, San Antonio.

**Short-term studies.** The first 2 weeks were a single-blind placebo period during which the patients took three placebo tablets four times daily. Digoxin, \( \beta \)-blocker, and long-acting nitrate therapy was stopped. The third and fourth weeks were the randomized, double-blind crossover portion of the study. Patients took either three placebo or three 30 mg diltiazem tablets four times daily. Symptom-limited exercise treadmill tests were performed by the patients at the end of each week; on another day in week 3 and week 4 rest and exercise radionuclide angiograms were recorded.

**Long-term studies.** After completion of the short-term studies 12 patients consented to participate in the long-term study and were treated with 90 mg diltiazem four times a day for 16 weeks (weeks 5 through 20). Treadmill tests were performed at the end of weeks 12 and 20. During week 21 patients received placebo tablets in a fashion identical to that in the short-term study and performed exercise tests. Plasma samples for measuring diltiazem levels by high-performance liquid chromatography were obtained at the end of week 20.\(^{10}\) All patients had measurable diltiazem plasma levels, with a mean value of 171 ± 93 ng/ml. Two patients did not complete the long-term study, one because of sudden death and one because of the side effects of diltiazem. Thus, 10 patients completed the long-term study and are included in the data analysis.

**Exercise treadmill tests.** Exercise treadmill tests were performed with a modified Bruce protocol,\(^13\) the initial 3 min stage being at 1 mph and a 5% grade. Exhaustion or moderately severe angina pectoris were used as end points for termination of the test. All patients were encouraged to exercise until the onset of both angina pectoris and diagnostic ischemic ST segment depression. Leads II and V\(_5\) of the electrocardiogram were monitored continuously during exercise; a 12-lead electrocardiogram was obtained after each minute of exercise. Heart rate and blood pressure (cuff sphygmomanometer) were measured in the patients while supine, after 2 min of standing, after each minute of exercise, and during recovery.

Stress electrocardiograms were interpreted blindly; a positive test result was defined as 1 mV of horizontal or down-sloping ST segment depression for at least 80 msec after the J point in 3 consecutive beats in any of the anterolateral precordial leads.

**Catecholamine and lactate levels.** Paired venous blood samples were obtained in 11 patients for the determination of plasma norepinephrine, epinephrine, and lactate levels before and immediately after the treadmill exercise test during weeks 3 and 4. The paired plasma samples were analyzed in triplicate and the analyzer did not have access to the randomization code. Plasma norepinephrine and epinephrine levels were determined by the modified radioenzymatic method of Passen and Peuler\(^12\) (Upjohn Co.) and plasma lactate levels were measured enzymatically with the use of commercial reagent kits\(^13\) (Sigma Chemical).

**Radionuclide angiography.** Equilibrium radionuclide angiography was performed during weeks 3 and 4 of the short-term study while patients exercised on an upright bicycle ergometer. Studies were performed in fasting patients 2 to 4 hr after the preceding dose of study medication. In vivo blood pool labeling was performed by the injection of 20 to 21 mCi \( ^{99m} \text{Tc} \) pertechnetate 20 min after the intravenous injection of 1.7 mg stannous chloride. Exercise was performed in graded 150 kilopond-meter/min work stages of 3 min each.

Gated equilibrium blood pool studies were obtained with a portable, single-crystal, 37 photomultiplier–tube gamma camera equipped with a parallel-hole all-purpose medium-sensitivity colimator. Data were obtained with the camera in a 45 degree anterior oblique projection in patients at rest, seated on the bicycle, and during the last 2 min of each exercise stage.\(^14\) Radionuclide angiograms were analyzed by a semiautomated computer software program (Technicare Inc.) with smoothing, background subtraction, and automated determination of variable left ventricular regions of interest.\(^15\) Ejection fraction was determined by the ratio of stroke counts to end-diastolic counts. Left ventricular volumes were determined by the method of Links et al.\(^16,17\)

**Results**

**Exercise treadmill tests**

**Short-term trial.** There was a highly significant effect of diltiazem on the onset of ischemic ST segment depression, the onset of angina pectoris, and total exercise duration (figure 1). During the first 2 weeks on placebo, ST segment depression occurred at 427 ± 134 and 438 ± 121 sec, respectively. During randomization ST segment depression occurred at 447 ± 125 sec during placebo treatment and at 567 ± 160 sec during diltiazem therapy, for a mean improvement of 120 sec (p < .0001). Also during randomization the time to the onset of angina was 422 ± 113 sec with placebo and 596 ± 120 sec with diltiazem (a mean improvement of 174 sec, p < .0001). Two patients did not experience ST depression during the week they were treated with diltiazem, and two different patients had no exercise-induced angina during diltiazem therapy. During randomized placebo treatment peak exercise occurred at 527 ± 126 sec and during diltiazem therapy it occurred at 671 ± 116 sec; this represents a mean improvement during treatment with diltiazem of 144 sec (p < .0001).

**Long-term studies.** The onset of ischemic ST segment depression occurred at 497 ± 154 sec in week 12 and at 555 ± 153 sec in week 20; during week 21 (placebo) the time was 389 ± 84 sec (p < .01 compared to week 20). The onset of angina pectoris was 527 ± 101 sec during week 12, 561 ± 115 sec during week 20, and 375 ± 106 sec during week 21 (placebo) (p < .01). Peak exercise occurred at 591 ± 108 sec during week 12, 617 ± 138 sec during week 20, and 478 ± 99 sec during placebo treatment (week 21) (p < .001). Thus, the effects of diltiazem that were observed early persisted for 20 weeks and were not due to placebo effects (figure 2).
Resting and exercise catecholamine and lactate levels. In patients at rest the mean plasma norepinephrine level during placebo treatment was 498 ± 221 pg/ml, and during diltiazem therapy it rose to 667 ± 272 pg/ml (p < .05). During exercise plasma norepinephrine levels rose significantly (to 1295 ± 457 pg/ml) in patients on placebo (p < .0001) and in those on diltiazem therapy (to 2850 ± 1240 pg/ml, p < .0001). The exercise levels were significantly higher during the diltiazem treatment week than during the placebo week (p < .01). Similar changes were observed in epinephrine and lactate levels (table 1).

Hemodynamic response to exercise (table 2). Diltiazem produced no significant changes in resting supine or standing heart rates, or in the heart rates at each of the exercise end points. The mean systolic supine blood pressures in patients at rest showed no differences over the course of the short-term study, but diltiazem did potentiate the orthostatic decrease in systolic blood pressure by 7 mm Hg (p < .05). There were no differences in systolic blood pressures in patients on placebo and those on diltiazem at any of the exercise treadmill test end points. Resting supine and standing diastolic blood pressures were significantly lowered during diltiazem therapy (p < .01).

The heart rate–systolic pressure products measured with the patients standing on the treadmill immediately before exercise, at the onset of ST segment depression in the 11 patients with ST depression during all treadmill tests, at the onset of angina pectoris in the 11 patients with angina during all treadmill tests, and at peak exercise are illustrated in figure 3. Resting rate-pressure products were lower and exercise rate-pressure products higher during diltiazem therapy. The changes in rate-pressure product from rest to exercise are illustrated in figure 4. The rate-pressure product during diltiazem treatment decreased at rest and increased at ST depression, at angina pectoris, and at peak exercise. The net increase from rest to the exercise end points of angina and peak exercise was greater during therapy with diltiazem than during placebo treatment (p < .05).

Exercise radionuclide angiography (table 3). The time to the onset of ST segment depression, angina pectoris, and peak exercise showed parallel changes in patients on diltiazem during bicycle ergometry and during exercise treadmill testing. ST segment depression occurred at 430 ± 126 sec in patients on placebo and at 537 ± 153 sec in those on diltiazem (p < .0001) and angina pectoris occurred at 433 ± 108 sec in patients on placebo and at 592 ± 131 sec in those on diltiazem (p < .001). All patients experienced angina pectoris while on placebo, whereas five did not during treat-

**TABLE 1**
Plasma catecholamine and lactate levels in 11 patients at rest and during exercise

<table>
<thead>
<tr>
<th>Patients at rest</th>
<th>Norepinephrine (pg/ml)</th>
<th>Epinephrine (pg/ml)</th>
<th>Lactate (mg/dl)</th>
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<tr>
<td>Placebo</td>
<td>498 ± 221</td>
<td>38 ± 14</td>
<td>11.9 ± 3.7</td>
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<tr>
<td>Diltiazem</td>
<td>667 ± 272&lt;sup&gt;a&lt;/sup&gt;</td>
<td>47 ± 21</td>
<td>12.5 ± 5.4</td>
</tr>
<tr>
<td>During exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1295 ± 457</td>
<td>73 ± 40</td>
<td>22.5 ± 9.4</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>2850 ± 1240&lt;sup&gt;b&lt;/sup&gt;</td>
<td>170 ± 90&lt;sup&gt;c&lt;/sup&gt;</td>
<td>43.5 ± 9.3&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>p < .05; <sup>b</sup>p < .01; <sup>c</sup>p < .001 for placebo vs diltiazem.

**FIGURE 1.** Results of exercise treadmill tests in the 13 patients who completed the 4 week short-term study of diltiazem (360 mg/day). The graph depicts the time (in sec) until the onset of ischemic ST segment depression (ST < 1), angina pectoris (AP), and peak exercise (PK EX). Weeks 1 and 2 were the single-blind placebo (P) treatment weeks. Weeks 3 and 4, the randomized double-blind crossover weeks, are labeled "placebo" and "diltiazem." See text for mean values. ***p < .0001.
ment with diltiazem ($p < .01$). Peak exercise occurred at $515 \pm 129$ sec during placebo treatment and at $653 \pm 117$ sec during diltiazem therapy ($p < .001$).

The resting left ventricular ejection fraction was $52 \pm 11\%$ and increased to $58 \pm 11\%$ during treatment with diltiazem ($p < .001$). All five patients with resting ejection fractions of less than $50\%$ had increases in resting ejection fraction (2\% to 18\%) during diltiazem therapy. The ejection fraction at peak exercise during placebo treatment fell to $44 \pm 11\%$ ($p < .001$ compared with rest) and during diltiazem therapy it fell to $52 \pm 15\%$ ($p < .01$). The peak exercise ejection fraction during diltiazem therapy was significantly higher than that during placebo treatment ($p < .01$).

There was no significant difference in left ventricular volumes during the 2 treatment weeks either at rest or at peak exercise. The increase in end-diastolic volume from rest to peak exercise during radionuclide angiography was significant in patients on placebo and diltiazem therapy ($p < .0001$). Also, the increase in end-systolic volume produced by exercise was significant during both treatment periods ($p < .0001$).

**Complications.** Of the 13 patients completing the short-term trial, one experienced pedal edema without evidence of heart failure during the week of diltiazem treatment. Of the 12 patients in the long-term trial, five experienced pedal edema without evidence of heart failure. The edema occurred during the first 2 to 3 weeks of drug therapy. In three patients this was a transient phenomenon, but two patients have required a thiazide diuretic to control symptomatic edema. Five of the 13 (38\%) patients experienced edema at some point in the study.

One of the five patients with edema experienced
TABLE 2
Hemodynamic responses to exercise

|                     | Week 1 placebo | Week 2 placebo | Weeks 3 and 4 Placebo | Diltiazem | p^  
|---------------------|----------------|----------------|-----------------------|-----------|---  
| Heart rate (min^-1) |                |                |                       |           |    
| Supine              | 66±12          | 68±10          | 69±14                 | 64±10     | NS  
| Standing             | 78±13          | 78±13          | 79±16                 | 74±10     | NS  
| ST↓                 | 119±15         | 122±15         | 121±19                | 127±18    | NS  
| AP                  | 119±20         | 122±17         | 120±19                | 127±14    | NS  
| PK EX               | 129±17         | 130±14         | 126±121               | 134±17    | NS  
| Systolic BP (mm Hg) |                |                |                       |           |    
| Supine              | 138±19         | 138±17         | 137±18                | 134±17    | NS  
| Standing             | 135±19         | 135±16         | 137±16                | 128±15    | .05  
| ST↓                 | 170±30         | 171±23         | 171±27                | 171±24    | NS  
| AP                  | 170±30         | 169±28         | 170±21                | 173±29    | NS  
| PK EX               | 172±31         | 173±29         | 173±29                | 172±25    | NS  
| Diastolic BP (mm Hg) |                |                |                       |           |    
| Supine              | 85±9           | 80±10          | 80±11                 | 74±8      | .05  
| Standing             | 86±11          | 84±12          | 82±11                 | 76±10     | .01  
| Rate-pressure product (×10^-3) | | | | |  
| Standing             | 10.6±3.2       | 10.6±2.7       | 10.7±2.4              | 9.5±1.8   | NS  
| ST↓                 | 19.7±4.7       | 20.3±3.4       | 20.1±3.9              | 20.6±3.4  | NS  
| AP                  | 19.7±5.5       | 19.8±4.3       | 18.7±4.3              | 20.7±3.6  | NS  
| PK EX               | 22.2±5.2       | 22.7±5.0       | 21.9±5.4              | 23.2±5.1  | NS  
| Change in RPP to ST | (n = 11) | | | |  
|                     | 9.0±3.5        | 9.9±3.5        | 9.4±3.3               | 11.2±3.7  | NS  
| Change in RPP to AP | (n = 11) | | | |  
|                     | 9.1±2.9        | 9.2±3.6        | 8.2±2.9               | 11.1±3.2  | .05  
| Change in RPP to PK | | | | |  
| EX                  | 11.6±3.5       | 12.1±4.9       | 11.2±4.8              | 13.6±5.0  | .05  

^ST = 1 mV (measureable) ST segment depression; AP = angina pectoris; PK EX = peak exercise; RPP = heart rate–systolic pressure product.

Discussion

This study documents the efficacy of diltiazem (360 mg/day) for chronic exertional angina pectoris in patients with coronary artery disease. In comparison to previously reported studies of lower doses of diltiazem, we have demonstrated greater benefit with the higher dose, but also increased side effects.

Exercise tolerance. A triple crossover, placebo-controlled, double-blind, randomized trial on the effects of diltiazem at doses of 120, 180, and 240 mg/day on the exercise tolerance of patients with coronary artery disease demonstrated improved exercise treadmill performance at the dose of 240 mg/day only.3-6 The data from the 57 patients in these studies was summarized by Hossack et al.1 and showed that there was a mean 48 sec increase in the time to ST segment depression, a mean 38 sec increase in the time to angina pectoris, and a mean 49 sec increase in the time until peak exercise. Also, Strauss et al.8 reported a multicenter randomized double-blind study on the effects of diltiazem in 63 patients, but it was not of a crossover design. Beneficial effects by exercise treadmill testing could be demonstrated after 4 weeks, but not after 2 weeks, of therapy with diltiazem at a dose of 240 mg/day.

Randomized double-blind, single-dose trials have been conducted by Koiwaya et al.8 in patients receiving a 90 mg dose and by Wagniart et al.9 in patients receiving a 120 mg dose of diltiazem. Koiwaya et al. demonstrated a 144 sec improvement in time to ST segment depression, a 150 sec improvement in time to angina pectoris, and a 150 sec improvement in time to peak exercise. Wagniart et al. demonstrated a 170 sec improvement in time to ST segment depression and a 105 sec improvement in time to peak exercise. These data are comparable to the improvements we have found in patients on long-term diltiazem therapy of 360 mg/day in four 90 mg doses; the time to ST segment depression increased by 120 sec, the time to angina pectoris by 174 sec, and the time to peak exercise by 144 sec. After 20 weeks of therapy the benefits persisted, with a 166 sec improvement in time to ST segment depression, a 186 sec improvement in time to angina pectoris, and a 139 sec improvement in time to peak exercise.

Hemodynamic effects. Studies on the effects of diltiazem on resting and exercise heart rate in man have produced varied results. Kawai et al.19 and Bourassa et al.20 showed no effects of intravenous diltiazem on sinus rate. Also, after a single oral dose of diltiazem in postinfarction patients, Bourassa et al.20 demonstrated an 11% reduction in resting heart rates. Hossack and
Bruce\(^5\) have shown a significant reduction in resting and exercise heart rate after oral diltiazem. In addition, Strauss et al.\(^18\) showed a significant decrease in peak exercise heart rate in patients treated with diltiazem doses of 240 mg/day. The cases of four patients experiencing atrioventricular block during oral diltiazem therapy (240 to 360 mg/day) have been reported.\(^21\)

In patients with coronary artery disease significant changes in resting systolic and diastolic blood pressures have not often been demonstrated. Strauss et al.\(^18\) observed a reduction in diastolic blood pressure only of 9 to 10 mm Hg at peak exercise in patients taking 240 mg/day of diltiazem. Maeda et al.\(^22\) demonstrated significant reductions in systolic, diastolic, and mean blood pressures in a subgroup of hypertensive patients and the effects were potentiated by the addition of oral diuretics. Hossack et al.\(^23\) showed that 120 mg diltiazem produced significant decreases in mean arterial pressure and decreases in pulmonary artery wedge pressure in coronary artery disease patients with elevated resting wedge pressures. Our study demonstrates reductions in standing systolic blood pressure and supine and standing diastolic blood pressures in patients with stable angina given 360 mg/day.

Conflicting data on the effects of diltiazem on the heart rate–systolic blood pressure product during exer-

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\(\text{FIGURE 3. Heart rate–systolic blood pressure products at rest and at each exercise treadmill test end point for the 13 patients completing the short-term study. Abbreviations are as in figure 1.}\)

\(\text{FIGURE 4. Change in rate-pressure product from rest to each exercise treadmill test end point. The 11 patients with ST segment depression or angina pectoris on both randomized tests are included. All 13 patients are included in peak exercise values. Abbreviations are as in figure 1. } *p < .05.\)

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\(\text{PETRU et al.}\)
cise have been reported. Nakayama\textsuperscript{24} showed a decrease in resting rate-pressure products of $1.6 \times 10^3$ during therapy with 90 mg/day diltiazem. Bourassa et al.\textsuperscript{20} reported a 15% decrease in resting rate-pressure product after a single dose of 120 mg diltiazem in patients with coronary disease and recent myocardial infarction. Starling et al.\textsuperscript{7} reported a 15% increase in rate-pressure product at peak exercise in patients taking 240 mg/day diltiazem without a change in resting rate-pressure products. Wagniart et al.\textsuperscript{9} showed a 15% increase in rate-pressure product at the onset of ST segment depression in their patients receiving a single 120 mg dose of diltiazem, but no change in rate-pressure products at the termination of exercise or at rest. These data suggest that the rate-pressure product exercised to by patients on diltiazem is equal to or higher than that of patients receiving a placebo.

**Catecholamine and lactate levels.** This study is the first report of resting and exercise plasma catecholamine and lactate levels in patients taking diltiazem. The significant increase in resting norepinephrine levels during therapy with diltiazem raises several possibilities concerning the principal mode of action of diltiazem in patients with coronary artery disease. The increase in resting norepinephrine levels in conjunction with the significant reduction in blood pressure may reflect a baroreceptor-mediated increase in circulating norepinephrine. The alterations in catecholamine levels we observed may be related to other effects of calcium-channel blockade, including modulation of catecholamine receptor number, physiology, and distribution. The potential interaction of diltiazem and other calcium-channel blockers with $\alpha$- and $\beta$-adrenergic receptors has not been well defined in patients with coronary artery disease.\textsuperscript{25}

**Exercise radionuclide angiography.** Left ventricular ejection fractions at rest and at peak exercise showed significant increases during diltiazem therapy and these improvements occurred in patients with or without depressed resting left ventricular ejection fractions. In a double-blind study, Low et al.\textsuperscript{6, 26} performed radionuclide angiograms in patients at rest who were taking 240 mg/day diltiazem. Compared with the corresponding placebo week, there was a significant increase in resting left ventricular ejection fraction from 50% to 54% ($p < .05$). Left ventricular performance during exercise was not evaluated.

The effects of verapamil on left ventricular function have been evaluated in patients with coronary disease during exercise. Sadick et al.\textsuperscript{27} used exercise radionuclide angiography and demonstrated no significant change in resting ejection fraction in 18 patients treated....

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**TABLE 3**

Radionuclide angiography

<table>
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<tr>
<th>Patient No.</th>
<th>Ejection fraction (%)</th>
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<th>End-systolic volume (ml)</th>
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<tr>
<td>p (Pl vs D\textsuperscript{d})</td>
<td>&lt;.001</td>
<td>&lt;.01</td>
<td>NS</td>
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</table>

EX = peak exercise.

\textsuperscript{a}No angina.

\textsuperscript{b}No ST depression.

\textsuperscript{c}Rest vs exercise.

\textsuperscript{d}Placebo vs diltiazem.
with placebo, propranolol, or verapamil. The mean left ventricular ejection fraction decreased with exercise in patients on placebo, increased with exercise in those on propranolol, and increased with exercise in those on verapamil. Exercise tests were intentionally set at 50% and 75% of the maximal work load accomplished during the baseline study. Thus, in these patients who did not have angina or positive exercise test results during radionuclide angiography, the data represent left ventricular performance at subischemic work loads. In distinction, our protocol was designed to obtain radionuclide angiograms during active myocardial ischemia; we observed a fall in ejection fraction at peak exercise in patients on diltiazem and those on placebo.

Our data suggest that improved left ventricular systolic performance in patients taking diltiazem may be partially due to decreases in systolic and diastolic blood pressures. Diltiazem produces only minimal negative inotropic effects during intravenous and intracoronary administration in dogs, even in high doses. There were no changes in resting or peak exercise end-diastolic volumes; therefore, alterations of contractility and wall stress may not be the key factors in improving the imbalance between myocardial oxygen demand and supply in patients treated with diltiazem. However, at peak exercise in patients receiving diltiazem we found no significant decrease in blood pressure, rate-pressure product, or heart rate. Also, we found no significant change in end-diastolic volume or hemodynamic measures at peak exercise in patients taking diltiazem compared with those on placebo. The benefit seen with diltiazem during exercise may be related to favorable alterations in myocardial blood flow or aortic impedance or to alterations in oxygen consumption. Further investigations will be needed to delineate the mechanism(s) mediating improved exercise performance during therapy with diltiazem.

Complications and adverse effects. Because peripheral edema has been reported in patients taking nifedipine and verapamil, we were not surprised to find this side effect in patients taking diltiazem. However, ours is the first report of a high incidence of peripheral edema during diltiazem therapy. As reported by Kinoshita et al., the mechanism of this effect may be related to altered sodium excretion. The edema we observed, although common, was not a clinical problem requiring dose reduction.

In a placebo-controlled, randomized, double-blind crossover study we examined the effects of oral diltiazem (360 mg/day) on treadmill exercise performance, hemodynamic variables during exercise, and exercise radionuclide angiography. There was a significant improvement in exercise tolerance that was greater than that seen in patients in previous studies who were taking 240 mg/day of diltiazem. Resting and peak exercise ejection fractions were significantly higher during therapy with diltiazem, despite possible negative inotropic effects, and probably resulted from decreased left ventricular afterload. The drug was well tolerated in most patients, despite the common side effect of peripheral noncardiogenic edema. The mechanism of improvement in cardiac function during diltiazem therapy remains unknown, but is likely related to both a decrease in the parameters determining myocardial oxygen consumption and an improvement in blood flow to areas of myocardial ischemia.

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References


Short- and long-term efficacy of high-dose oral diltiazem for angina due to coronary artery disease: a placebo-controlled, randomized, double-blind crossover study.

M A Petru, M H Crawford, S G Sorensen, T K Chaudhuri, S Levine and R A O'Rourke

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