The effect of diltiazem and propranolol, alone and in combination, on exercise performance and left ventricular function in patients with stable effort angina: a double-blind, randomized, and placebo-controlled study

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ABSTRACT The effects of oral diltiazem and propranolol, alone and in combination, were compared with those of placebo in 12 patients with stable effort angina. Patients performed symptom-limited, multistage, upright bicycle ergometric exercise while undergoing equilibrium-gated radionuclide angiographic examination after 2 week periods of 90 mg diltiazem four times daily, 60 mg propranolol four times daily, a combination of 90 mg diltiazem and 60 mg propranolol four times daily, and placebo. All drugs were given double blind and in randomized order. Diltiazem, propranolol, and the combination significantly increased exercise duration compared with placebo (562 ± 149, 525 ± 115, and 549 ± 121, vs 430 ± 132 sec); the drugs also increased time to onset of angina pectoris and ischemic (≥ 1 mm) ST segment depression (all p < .05). Compared with after placebo, heart rate and rate-pressure product at a fixed submaximal workload were decreased after diltiazem (both p < .05), but were unchanged at peak effort. Heart rate and rate-pressure product at both submaximal and peak effort were decreased by propranolol (all p < .001) and were decreased further by the combination of diltiazem and propranolol (all p < .05 vs propranolol). Diltiazem and the combination of diltiazem and propranolol decreased maximal exercise ST segment depression (both p < .01 vs placebo). The mean exercise left ventricular ejection fraction was higher in patients on diltiazem than in those on placebo, propranolol, or the combination of diltiazem and propranolol (all p < .05). Adverse side effects severe enough to require dosage reduction (severe sinus bradycardia or orthostatic hypotension) occurred in four patients on combination therapy. High-dose diltiazem alone appears to be as effective as or more effective than moderate-dose propranolol or the combination of diltiazem and propranolol in improving exercise tolerance, myocardial ischemia, and left ventricular function in patients with stable effort angina.


CALCIUM-CHANNEL BLOCKERS provide a promising alternative to β-blockers for the management of patients with exertional angina and fixed coronary artery disease. These drugs can reduce myocardial oxygen demand by decreasing systemic vascular resistance, and in some cases cardiac contractility and heart rate, while producing an increase in coronary blood flow through dilation of large coronary vessels.1–2 The results of some studies have also suggested that the combination of these drugs with β-blockers may be an effective antianginal regimen in patients with medically refractory disease.3–5 However, calcium-channel blockers are not equipotent in their systemic vascular, coronary vascular, myocardial, or electrophysiologic effects6–9 and therefore may differ in their primary antianginal mechanisms and in their interactions with β-blocking drugs.

Diltiazem is a potent coronary dilator that has been documented to be highly effective in the prevention of vasospastic angina and it produces only a low incidence of side effects.10–12 Unlike nifedipine, which commonly causes reflex tachycardia at rest, diltiazem may have a negative chronotropic effect1–9 that could
be beneficial in angina patients because it reduces myocardial oxygen demand. In vitro diltiazem has less negative myocardial inotropic effects and in man it causes suppression of sinoatrial and atrioventricular nodal function less than or equal to that caused by verapamil. Consequently, the combination of diltiazem with a β-blocker may be relatively safe, although this has not been previously studied. The effects of diltiazem are also dose dependent. In patients with stable effort angina, an increase in exercise tolerance and a negative chronotropic effect of diltiazem are more evident at higher doses, but the effects of doses larger than 240 mg/day (or 60 mg four times daily) have not been previously studied. The specific objective of this study was to compare the effects of 90 mg diltiazem four times daily, 60 mg propranolol four times daily, and the combination of diltiazem and propranolol with those of placebo on exercise performance, myocardial ischemia, and left ventricular function in patients with stable exertional angina. Secondary objectives were to determine if there were any differences in the antianginal mechanisms of the drugs and to assess the short-term safety of high-dose diltiazem, both alone and in combination with propranolol.

Methods

Patients. Patients with a history of stable exertional angina pectoris were considered for entry into the study. Inclusion was dependent on demonstrating classical angina pectoris and 1 mm or greater horizontal or down-sloping ST segment depression during multistage upright bicycle ergometer testing. Patients who had had clinical congestive heart failure, unstable angina pectoris, or myocardial infarction within the past 6 months were excluded, as were patients in whom all active cardiac drugs, excepting sublingual nitroglycerin, could not be withdrawn before the study and those who had significant noncardiac limitations to exercise, such as chronic obstructive airway or peripheral vascular disease. Twelve patients (11 men and one woman; mean age 61 years, range 50 to 68) gave written informed consent to participate in this study. Coronary arteriography had been performed for severe angina in 11 of these subjects and showed 70% or more stenosis in two or three vessels. Six patients had had prior coronary artery bypass surgery. No patients had a past history of myocardial infarction. Data from three other patients were excluded from analysis because they were unable to complete the protocol, one because of deterioration of previous retinal detachment that excluded further exercise testing, another because of recurrence of atrial fibrillation when the usual dose of digoxin was withdrawn, and a third because of development of orthopedic problems that limited exercise test tolerance.

Experimental protocol. Each patient underwent therapy for four consecutive 2 week periods with diltiazem, propranolol, the combination of diltiazem and propranolol, and placebo for 2 weeks each. The order of drug treatment was randomized by a 4 × 4 Latin square design. On the first day of each treatment period the patients were given 30 mg diltiazem four times daily, 20 mg propranolol four times daily, a combination of these doses, or placebo. The dose was doubled after 24 hr and tripled after another 24 hr to 90 and 60 mg four times daily of diltiazem and propranolol, respectively, or a combination of these doses. The use of identical placebo, diltiazem, and propranolol tablets ensured that the treatments seemed identical to the patients at all times. On each day of dose titration, at 3 hr after pill intake, each patient transmitted transtelephonically (Cardiobeeper, Survival Technology) a resting (standing or sitting) electrocardiographic tracing (MCLS). If a dose-related adverse effect was observed (sinus bradycardia less than 45 beats/min, second or higher degree atrioventricular block, symptomatic hypotension, or orthostatic dizziness) the dose was reduced to the next lowest tolerable dose, which was then used through the rest of the treatment period. Exercise testing was performed on the morning of day 13 of each treatment period. After the exercise test, drug doses were titrated down over the next 36 hr before commencement of the next treatment period. All drugs were dispensed by the Pharmaceutical Division of Marion Laboratories, Inc., Kansas City, MO, which kept the treatment codes. These codes were not known by the patients or investigators until completion of the study.

Exercise testing. Multistage upright bicycle ergometer testing was combined with the recording of equilibrium-gated radionuclide angiograms. Exercise testing was performed with the patient in a fasting state at approximately the same time of the morning of each treatment period (3 hr [2.5 to 3.5] after the last dose of study medication). The gamma camera (Ohio Nuclear Series 120), which was equipped with a high-sensitivity collimator, was positioned for cardiac imaging in the left anterior oblique projection with the patient sitting upright on a Schwinn electrically braked bicycle ergometer. A specially constructed Lucite brace attached to the gamma camera was used to constrain the torso during exercise. In vivo red cell labeling was achieved by the method of Pavel et al. After an intravenous injection of 15 to 20 mCi 99mTc preceeded by stannous pyrophosphate, cycle ergometric exercise was started at a workload of 150 kg-m/min, increasing by 150 kg-m/min every 3 min until patients developed moderately severe angina, severe dyspnea, or fatigue. Other exercise end points included a systolic blood pressure drop of 10 mm Hg or more from the level in the preceding exercise stage or the development of ventricular tachycardia, that is, three or more consecutive ventricular extrasystoles. A 12-lead electrocardiogram was recorded in patients at rest, after each minute of exercise, and for 5 min during recovery. (Ischemic ST segment depression was defined as horizontal or downsloping ST segment depression of 0.1 mV or greater 80 msec after the J junction.) Heart rate counted from the electrocardiogram and arterial pressure (cuff sphygmomanometer) were determined in the last 15 sec of each exercise stage and at peak effort. Radionuclide data were collected on an Informatik Simis IV computer for later processing with previously described algorithms. In brief, radionuclide data were combined for 4 min of rest and for each exercise stage, provided the patient completed at least 2 min of the exercise stage. Data were analyzed automatically, that is, independent of the operator, by a series of algorithms that determined thresholding and left ventricular region of interest. Left ventricular ejection fraction was calculated by the standard formula from the background-subtracted left ventricular end-diastolic and end-systolic counts derived from the left ventricular time activity curve.

Laboratory determinations. A venous sample was collected 15 min before each exercise test for determination of plasma levels of diltiazem and propranolol. The plasma propranolol was assayed at Duke University Medical Center, Durham, NC, by a high-performance liquid chromatographic method. This assay was sensitive to 10 ng/ml propranolol in plasma and linear to at least 200 ng/ml. The plasma diltiazem was assayed at Marion Laboratories, Inc., by a high-performance liquid chro-
mographic method. This assay was sensitive to 10 ng/ml diltiazem in plasma and was linear up to 1500 ng/ml.

Statistical analysis. Multiple comparisons were made by analysis of variance and if statistical significance was found paired t testing was used for comparisons between two treatments. Frequencies were compared with the McNemar test for correlated proportions with Yates correction for one degree of freedom.

Results

Adverse effects. No complications resulted from exercise testing in the 12 patients. Also, no significant adverse effects were noted in patients taking placebo, diltiazem, or propranolol alone. Adverse effects were noted in five patients at the highest dose level of the combination of diltiazem and propranolol. Three patients had a resting sinus bradycardia of less than 45 beats/min (38, 42, and 40 beats/min); one of these patients also had orthostatic dizziness but two were asymptomatic. Resting heart rate on propranolol alone in these three patients was 47, 45, and 49 beats/min. Another patient had orthostatic dizziness and a standing blood pressure of 80/64 mm Hg at a heart rate of 54 beats/min. These adverse effects responded to a one-tablet reduction in dose of each drug; the diltiazem dose was reduced to 240 mg and the propranolol dose to 160 mg/day and these reductions were maintained for the duration of the treatment period. In a fifth patient, previously unsuspected short sinoatrial pauses were noted on the resting electrocardiographic trace on the day of the exercise test, but average sinus heart rate remained above 50 beats/min. This arrhythmia was not detected during subsequent treatment periods.

Exercise tolerance and ischemic responses. Analysis of variance indicated no significant test-order effect. Figure 1 illustrates the frequency of exercise-induced angina pectoris and ischemic ST segment depression after each of the four treatment periods. Exercise-induced angina pectoris occurred in all 12 patients on placebo and was associated with ischemic ST segment depression in 11. Angina pectoris was absent during exercise in six of the 12 patients on diltiazem and the combination of diltiazem and propranolol (both p < .05 vs placebo). Ischemic ST segment depression during exercise was also absent in six of 12 patients after diltiazem and in eight of 12 patients after the combination of diltiazem and propranolol (both p < .05 vs placebo). After propranolol the incidence of exercise-induced angina pectoris or ischemic ST segment depression was not significantly less compared with after placebo, being absent in only four and two of 12 patients, respectively. Either exercise-induced angina pectoris or ischemic ST segment depression occurred in eight, 11, and eight patients after diltiazem, pro-

![Figure 1](http://circ.ahajournals.org/lookup/fig/0)

**FIGURE 1.** The percent frequency of exercise angina pectoris and ischemic ST segment depression for the four treatments. The number of patients is denoted above each bar.

pranolol, and the combination, respectively; this was not a significant improvement over results in the placebo period. Exercise hypotension occurred in one patient each on placebo, diltiazem, and the combination of diltiazem and propranolol; exercise-induced ventricular tachycardia was not observed.

Figure 2 shows the total exercise duration and the time to the onset of angina pectoris and ischemic ST segment depression (≥ 1 mm) after each of the four treatments. Diltiazem, propranolol, and the combination of diltiazem and propranolol all increased total exercise duration (and hence peak workload) compared with placebo (mean ± SD = 526 ± 149, 525 ± 115, and 549 ± 121 vs 430 ± 132 sec, respectively; all p < .05). The drug treatments also increased the time to the onset of angina pectoris or to peak effort, if angina were absent, compared with placebo (506 ± 190, 470 ± 141, and 514 ± 148 vs 342 ± 127 sec, respectively; all p < .05) and the time to onset of ischemic ST segment depression or to peak effort (532 ± 150, 479 ± 138, and 524 ± 94 vs 350 ± 140 sec, respectively; all p < .01). Average exercise duration and time to ischemia was not significantly different among patients on diltiazem, propranolol, and the combination of diltiazem and propranolol.

Effect on exercise hemodynamics. Changes in heart rate, systolic blood pressure, rate-pressure product, left ventricular ejection fraction, and ST segment depression during the four treatment periods are listed in table 1. Heart rate and rate-pressure product during exercise are plotted against exercise duration in figure 3. Compared with placebo, diltiazem decreased heart
rate at rest and at a fixed submaximal workload (300 kg-m/min; both $p < .001$), but not at peak exercise. Systolic blood pressure at rest and during exercise was not reduced by diltiazem. Because of the reduction in heart rate, diltiazem caused a decrease (vs. placebo) in rate-pressure product at rest and at submaximal effort (both $p < .05$), although not at peak effort. Compared with placebo, propranolol markedly decreased heart rate ($p < .001$) and systolic pressure ($p < .05$) at rest and at submaximal and peak effort. Consequently, rate-pressure product was markedly reduced by propranolol at rest and throughout exercise (all $p < .01$ vs placebo and diltiazem; table 1, figure 3). The combination of diltiazem and propranolol further reduced heart rate, systolic pressure, and rate-pressure product at rest and at submaximal and peak exercise (all $p < .05$ vs propranolol; table 1, figure 3).

**Effect on electrocardiographic evidence of ischemia.** The relationship between the magnitude of ST segment depression and rate-pressure product is illustrated in figure 4. Despite an unchanged peak rate-pressure product, the average maximal exercise ST segment depression was half as much in patients on diltiazem as in those on placebo ($p < .05$; table 1). Propranolol produced a smaller reduction in the magnitude of ST segment depression at peak effort ($p < .05$ vs placebo), despite a much greater reduction in peak rate-pressure product. Patients on the combination of diltiazem and propranolol had the least amount of ischemic ST segment depression; at peak effort it was only one-third of that seen after propranolol alone ($p < .01$).

**Effect on left ventricular function.** The mean resting left ventricular ejection fraction in the 12 patients during placebo was 59% (range 35% to 71%) and was less than 50% in two patients (35% and 40%). Left ventricular ejection fraction is plotted against the rate-pressure product reached during exercise in figure 5. The mean exercise left ventricular ejection fraction was higher during diltiazem than during placebo, propranolol, or the combination of diltiazem and propranolol.

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**TABLE 1**

Rest and exercise data for patients on diltiazem, propranolol, and their combination

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>SBP (mm Hg)</th>
<th>RPP (x 100)</th>
<th>LVEF (%)</th>
<th>ST depression (mm)</th>
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</thead>
<tbody>
<tr>
<td><strong>Resting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Placebo</td>
<td>81 ± 16</td>
<td>132 ± 28</td>
<td>109 ± 37</td>
<td>59 ± 14</td>
<td>0.3 ± 0.6</td>
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<td>Diltiazem</td>
<td>70 ± 14$^c$</td>
<td>126 ± 18</td>
<td>89 ± 24$^A$</td>
<td>63 ± 12</td>
<td>0.0 ± 0.0</td>
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<tr>
<td>Propranolol</td>
<td>56 ± 9$^c$</td>
<td>130 ± 19</td>
<td>74 ± 22$^c$</td>
<td>52 ± 10$^b$</td>
<td>0.1 ± 0.3</td>
</tr>
<tr>
<td>Combination</td>
<td>54 ± 11$^c$</td>
<td>114 ± 19$^a$</td>
<td>62 ± 19$^c$</td>
<td>53 ± 8$^b$</td>
<td>0.0 ± 0.0</td>
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<tr>
<td><strong>Submaximal effort</strong> (300 kg-m/min)</td>
<td></td>
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<td></td>
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<tr>
<td>Placebo</td>
<td>111 ± 19</td>
<td>157 ± 22</td>
<td>176 ± 45</td>
<td>55 ± 19</td>
<td>1.4 ± 1.1</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>99 ± 19$^c$</td>
<td>160 ± 25</td>
<td>160 ± 41$^A$</td>
<td>64 ± 17$^a$</td>
<td>0.3 ± 0.6$^b$</td>
</tr>
<tr>
<td>Propranolol</td>
<td>80 ± 14$^c$</td>
<td>144 ± 17$^A$</td>
<td>117 ± 32$^c$</td>
<td>53 ± 11</td>
<td>0.5 ± 0.6$^a$</td>
</tr>
<tr>
<td>Combination</td>
<td>73 ± 11$^c$</td>
<td>133 ± 20$^b$</td>
<td>98 ± 26$^c$</td>
<td>53 ± 11</td>
<td>0.1 ± 0.3$^b$</td>
</tr>
<tr>
<td><strong>Peak effort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>122 ± 20</td>
<td>167 ± 25</td>
<td>205 ± 50</td>
<td>52 ± 18</td>
<td>2.1 ± 1.3</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>117 ± 14</td>
<td>175 ± 26</td>
<td>204 ± 34</td>
<td>59 ± 19</td>
<td>1.0 ± 0.8$^a$</td>
</tr>
<tr>
<td>Propranolol</td>
<td>91 ± 13$^c$</td>
<td>151 ± 20$^b$</td>
<td>139 ± 34$^c$</td>
<td>53 ± 13</td>
<td>1.5 ± 0.9$^a$</td>
</tr>
<tr>
<td>Combination</td>
<td>84 ± 9$^c$</td>
<td>143 ± 21$^b$</td>
<td>122 ± 29$^c$</td>
<td>55 ± 15</td>
<td>0.5 ± 0.7$^c$</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
SBP = systolic blood pressure; RPP = rate-pressure product; LVEF = left ventricular ejection fraction.

$^p < .05$ vs placebo; $^a p < .01$ vs placebo; $^b p < .001$ vs placebo.
HUNG et al.

FIGURE 3. Resting and exercise heart rate (top) and rate-pressure product (bottom) plotted against exercise duration for the four treatments. Values expressed are mean ± SEM.

(p < .05), but this difference was most significant at the submaximal-exercise stage. The changes in ejection fraction from rest to peak exercise were not significantly different after diltiazem and after placebo, although patients exercised to a higher peak work level after diltiazem (−4 ± 12% vs −7 ± 11%; table 1). The mean resting left ventricular ejection fraction was lower in patients on propranolol or the combination of diltiazem and propranolol than in those on placebo (both p < .05), but the change in ejection fraction from rest to peak exercise was more pronounced (1 ± 7% and 2 ± 8% vs −7 ± 11%, respectively; both p < .05). Diltiazem, propranolol, or their combination did not produce any further depression of resting left ventricular ejection fraction in the two patients with subnormal values on placebo. In one of the patients, who had a resting left ventricular ejection fraction of 40% on placebo, this value increased to 55% on diltiazem and was 45% on the combination of diltiazem and propranolol.

Blood levels. On diltiazem alone the mean plasma diltiazem concentration was 248 ng/ml (range 74 to 454) and in combination with propranolol it was 235 ng/ml (range 81 to 506). On propranolol alone the mean plasma propranolol concentration was 118 ng/ml (range 64 to 183) and in combination with diltiazem it was 109 ng/ml (range 23 to 180). Mean plasma levels of diltiazem and propranolol during combination therapy were not significantly different from their respective values during single-drug therapy.

Discussion
Studies of diltiazem in which single13-16 or repeated doses17-19 were used in patients with stable effort angina have shown a more marked effect with increasing dosage. Thus, Low et al.18 found no increase in exercise capacity with doses of less than 240 mg/day, while Hossack et al.17, 19 demonstrated continued improve-

FIGURE 4. The magnitude of ST segment depression plotted against rest and exercise rate-pressure product for the four treatments.

FIGURE 5. Resting and exercise left ventricular ejection and the corresponding rate-pressure product at which they were measured for the four treatments. Values expressed are mean ± SEM.
ment in exercise capacity with an increase in dose levels from 120 mg to 240 mg/day. Single-dose studies in which as much as 120 mg diltiazem was used\textsuperscript{15, 16} have shown no associated significant adverse effects. Consequently, we wanted to examine the short-term safety and efficacy of high-dose diltiazem (90 mg four times daily) in patients with stable effort angina. Also, we wanted to determine if the combination of diltiazem and propranolol could produce further beneficial effects.

Exercise testing was performed at approximately 3 hr after drug ingestion since peak plasma diltiazem and propranolol concentrations are reached in 3 to 4 hr.\textsuperscript{26, 27} Despite individual variation, the plasma diltiazem and propranolol concentrations were all in the therapeutic range,\textsuperscript{26, 27} and were not significantly different when the drugs were taken alone or in combination. Short-term use of 360 mg/day diltiazem in this study was not associated with any significant adverse effects. Its salutary effects included a 31% average increase in total exercise duration and a 52% average prolongation of time to the onset of ischemic ST segment depression. In addition, exercise-induced angina pectoris and ischemic ST segment depression were abolished in 50% of patients. While 240 mg/day propranolol also produced a significant increase in exercise duration, averaging 21%, the frequency of exercise-induced angina pectoris and ischemic ST segment depression was not significantly decreased. The combination of diltiazem and propranolol did not improve exercise duration more than diltiazem alone, even though ischemic electrocardiographic abnormalities were most frequently abolished by this combination. Peak exercise tolerance was most frequently limited by fatigue, probably as a consequence of the marked restriction in peak heart rate (84 ± 9 beats/min with the combination of drugs as opposed to 122 ± 20 beats/min with placebo and 117 ± 14 beats/min with diltiazem alone).

Antianginal mechanisms. High-dose diltiazem produced a modest reduction in heart rate and rate-pressure product at rest and submaximal effort that was similar to or somewhat larger than that reported for 240 mg/day diltiazem.\textsuperscript{17, 19} A reduction in submaximal rate-pressure product, an indirect index of myocardial oxygen demand,\textsuperscript{28} consequently allowed patients to work to a higher work level before the onset of ischemia. A decrease in myocardial oxygen demand appears to be the predominant antianginal mechanism for propranolol and the combination of diltiazem and propranolol since rest and exercise heart rate, systolic blood pressure, and rate-pressure product were all markedly decreased (figure 3). Examination of the relationship between ST segment depression and rate-pressure product illustrated in figure 4 indicates that for any given rate-pressure product, diltiazem produced less electrocardiographic ischemia than placebo. Hossack et al.\textsuperscript{15} also found this relationship in their study of exertional angina patients given single 120 mg doses of diltiazem. The addition of diltiazem to propranolol therapy also caused a two-thirds decrease in the amount of maximal ST segment depression observed in patients on propranolol alone. The reason(s) for the reduction of electrocardiographic ischemia with diltiazem is uncertain at the present time. Diltiazem has been shown to increase resting coronary blood flow in man\textsuperscript{29} and to increase blood flow to the subendocardium and border ischemic zones in the presence of flow-limiting stenosis in animals.\textsuperscript{30, 31} Against the hypothesis that diltiazem actually increased myocardial oxygen supply is the fact that peak rate-pressure product was the same for those on diltiazem and those on placebo. Diltiazem may reduce ischemic injury currents by improving intracellular calcium homeostasis in the presence of ischemia.\textsuperscript{32} Also, if diltiazem produces a reduction in ventricular volume and cardiac inotropic state, this could cause reduction in myocardial oxygen demand that is not reflected in the rate-pressure product. The fact that measured left ventricular ejection fraction was actually higher after diltiazem is not only evidence against a negative inotropic effect but is further evidence that diltiazem reduced the extent of myocardial ischemia.

Effect on left ventricular function. Diltiazem increased the levels of resting and exercise left ventricular ejection fraction when compared with placebo even though the change in ejection fraction from rest to peak exercise was qualitatively similar (figure 5). The augmentation of left ventricular ejection fraction was significant and most marked at submaximal exercise. Low et al.\textsuperscript{18} also measured resting left ventricular ejection fraction by radionuclide angiography in patients taking 240 mg/day of diltiazem and demonstrated a small but significant increase. Exercise left ventricular ejection fractions were not measured in their study. In vitro and in equihtensive doses, diltiazem produces less depression of ventricular muscle than either verapamil or nifedipine.\textsuperscript{7} Our study results demonstrate that in vivo high-dose diltiazem does not produce any significant left ventricular dysfunction and may actually increase left ventricular systolic function, probably as a consequence of a reduction in aortic impedance to left ventricular outflow.\textsuperscript{15, 18} Propranolol produced an average 7% reduction in resting left ventricular ejection fraction that, although statistically significant, was not
associated with clinically manifest left ventricular dys-
function. However, this may suggest that diltiazem is a
safer drug than moderate-dose β-blockers in angina
patients with depressed left ventricular function. Nev-
evertheless we found that, despite the lower resting eje-
tion fraction, the rest-to-exercise change in ejection
fraction was improved by propranolol when compared
with placebo, as noted by others.33, 34 This is probably
because of the reduction in peak rate-pressure product.
An important finding of our study was that the combi-
nation of diltiazem and propranolol did not produce
any clinically significant left ventricular dysfunction and
the resting and exercise left ventricular ejection
fractions were in fact similar to those seen after pro-
pranolol alone. However, patients with congestive
heart failure were specifically excluded from this study
and all but two of the 12 patients had normal resting
left ventricular ejection fractions. In one of the two
patients with a subnormal resting ejection fraction, diltiazem
actually produced a significant improve-
ment.

Diltiazem and propranolol combination. The combina-
tion of diltiazem and propranolol could potentially im-
prove both sides of the myocardial oxygen supply/
demand equation. β-Blockers have most commonly
been combined with nifedipine, since nifedipine com-
monly causes a reflex tachycardia at rest, and several
studies have found a greater improvement in exercise
tolerance with the combination of propranolol and ni-
fedipine than either drug alone.3, 4 Concerns about the
combined negative inotropic effects of verapamil and
β-blockers and their depressant effects on sinoatrial
and atrioventricular nodal tissue have restricted use of
this combination. However, Leon et al.5 demonstrat-
ed, in a limited number of angina patients, that the
combination of verapamil and propranolol can be given
safely and can produce an additional improvement in
exercise performance. Diltiazem has electrophysi-
ologic properties similar to those of verapamil.8, 9 Al-
though no clinically significant depression of left ven-
tricular function was found in this study, high doses of
diltiazem and propranolol in combination did have a
potential for producing significant bradycardia and
systemic hypotension. These adverse effects were
noted in five of 12 patients, but each case responded to
a reduction in dosage of both diltiazem and proprano-
lol. Second degree or higher grade atrioventricular
block was not observed. The marked restriction in
heart rate may have been the reason that overall exer-
cise tolerance, despite less electrocardiographic isch-
emia, was not improved by combination therapy be-
yond the improvement produced by diltiazem alone.

This suggests either that smaller doses of propranolol
should be used when it is given in combination with
diltiazem — although this hypothesis could not be
tested within the confines of the present study — or
that high-dose diltiazem could be used in single-drug
therapy.

Therapeutic implications. Diltiazem, 360 mg/day, ap-
pears, over the short-term, to be a safe and effective
alternative to moderate doses of propranolol for the
primary treatment of patients with stable exertional
angina. Diltiazem increases exercise tolerance and
time to ischemia and reduces the frequency of angina
and the extent of electrocardiographic ischemia to an
extent equal to or greater than moderate-dose propr-
anolol. Exercise left ventricular ejection fraction was
also improved by diltiazem. The addition of proprano-
lol to diltiazem therapy produced no further improve-
ment in exercise tolerance but did produce further re-
duction in electrocardiographic evidence of ischemia.
Careful titration of doses during combination therapy
is required because of additive depressant effects on
heart rate and blood pressure. However, high-dose
diltiazem alone appears to be equally effective for pa-
tients with stable effort angina.

We are grateful to D. G. Shand of Duke University Medical
Center, Durham, NC, for performing propranolol assays and to
Dan C. Dimmitt of Marion Laboratories, Inc., Kansas City,
MO for performing diltiazem assays. We would like to thank
Linda Beier, R.N., for technical assistance and Marie Hu,
M.A., for help with statistical analysis.

References
1. Stone PH, Antman EA, Muller JE: Calcium channel blocking
agents in the treatment of cardiovascular disorders: II. He-
odynam ic effects and clinical applications. Ann Intern Med 93: 886,
1980
2. Parisi AF, Strauss WE, McIntyre KM, Sasahara AA: Consider-
ations in evaluating new antianginal drugs. Circulation 65(supp 1):
I-38, 1982
3. Ekelund L-G, Oré L: Antianginal efficiency of nifedipine with and
without a beta-blocker, studied with exercise test. A double-blind,
randomized subacute study. Clin Cardiol 2: 203, 1979
5. Leon MB, Rosing DR, Bonow RO, Lipson LC, Epstein SE: Clini-
cal efficacy of verapamil alone and combined with propranolol in
treating patients with chronic stable angina pectoris. Am J Cardiol
48: 131, 1981
6. Henry PD: Comparative pharmacology of calcium antagonists:
7. Millard RW, Lathrop DA, Grupp G, Ashraff M, Grupp IL, Schwartz S:
Differential cardiovascular effects of calcium channel blocking
8. Kawai C, Konishi T, Matsuyama E, Okazaki H: Comparative effects of
two calcium antagonists, diltiazem, verapamil and nifedipine,
on sinoatrial and atrioventricular nodes. Experimental and
9. Mitchell LB, Schroeder JS, Mason JW: Comparative clinical elec-
trophysiologic effects of diltiazem, verapamil and nifedipine: a
review. Am J Cardiol 49: 629, 1982

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J Hung, I H Lamb, S J Connolly, K R Jutzy, M L Goris and J S Schroeder

_Circulation_. 1983;68:560-567
doi: 10.1161/01.CIR.68.3.560

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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