
A Double-blind Randomized Trial of Propranolol and Verapamil in the Treatment of Effort Angina


SUMMARY In 18 patients with stable effort angina, verapamil, 80 mg four times daily, was compared with propranolol, 80 mg four times daily, in a double-blind, placebo-controlled trial to assess the effects on anginal threshold, exercise capacity and left ventricular function measured by gated equilibrium blood pool scanning. Both propranolol and verapamil improved exercise capacity (placebo 424 ± 135 W·min; propranol 512 ± 168 W·min, p < 0.01; verapamil 545 ± 215 W·min, p < 0.005) and prolonged the time to 1 mm of ST depression (placebo 4.5 ± 1.3 minutes; propranolol 7.4 ± 1.4 minutes, p < 0.005; verapamil 6.6 ± 1.9 minutes, p < 0.005). At rest, the mean left ventricular ejection fraction did not change significantly during drug therapy (placebo 57 ± 13%, propranolol 55 ± 12%, verapamil 55 ± 13%). While taking placebo, all 18 patients had a decrease in exercise ejection fraction. In contrast, 12 patients taking propranolol and 14 patients taking verapamil had a 5% or greater increase in ejection fraction during exercise. Verapamil is an effective primary therapy and a satisfactory alternative to propranolol in patients with stable effort angina.

BETA-blockade therapy is effective in patients with effort angina. The mode of action is mainly due to a decrease in myocardial oxygen consumption, but side effects are common. Verapamil also relieves effort angina. The mode of action of verapamil is not fully understood, but side effects even at high dosage are uncommon. Objective studies comparing the effects of B blockers with those of verapamil in the treatment of stable effort angina are few.

We performed a double-blind, placebo-controlled study, using intrapatient comparisons, of the antianginal effects of oral propranolol (320 mg/day) and oral verapamil (320 mg/day) to measure the effects of these drugs on left ventricular function at rest and during exercise, and to determine whether the plasma drug concentrations were related to the physiologic changes produced.

Methods

Patient Population

Eighteen patients (17 males and one female), mean age 53 years (range 40–66 years), participated in the study. The entry criteria included a typical history of effort angina with no change in anginal pattern during the 3 months before entry into the study, two or more episodes of typical exertional angina per week, and a positive exercise test (defined as 1 mm of flat or downsloping ST depression for 0.08 second in three consecutive beats accompanying exercise-induced angina). Patients with clinical features of coronary artery spasm, recent episodes of nocturnal or prolonged chest pain at rest, hypertension, congestive cardiac failure, asthma, diabetes or abnormalities in resting ECG that made interpretation of ST-segment changes difficult (e.g., left ventricular hypertrophy or left bundle branch block) were excluded. Fourteen patients had New York Heart Association class II angina and four
patients had class III angina. Six patients had a history of myocardial infarction and five patients had electrocardiographic evidence of a previous transmural infarction. Ten patients who underwent coronary arteriography had significant coronary artery disease (defined as $>75\%$ diameter narrowing in one or more vessels). Three patients had three-vessel, two had two-vessel and five had one-vessel disease.

**Trial Design**

All previous therapy was ceased for the duration of the trial, except for short-acting nitrates. A 2-week, open run-in placebo phase was followed by three 3-week, double-blind treatment phases (fig. 1). A "double-dummy" technique with 80-mg tablets was used to ensure that treatment in all phases was visually identical. The treatments were propranolol, 320 mg/day, verapamil, 320 mg/day, or the placebo equivalent. The order of the double-blind treatments was determined by a $3 \times 3$ Latin-square design with six replications. At the start of each treatment period, the dosage was gradually increased so that by the fourth day the patient was taking the full dosage. Each treatment period was followed by a 3-day washout period. All 18 patients completed all three phases of the trial. Informed consent was obtained from all patients.

**Subjective Assessment**

Patients were discouraged from using glyceryl trinitrate prophylactically during the trial but were instructed to use it to relieve symptoms. The number of anginal attacks in the last 2 weeks of each 3-week treatment phase was recorded in a diary. After each treatment phase, all patients completed a questionnaire on side effects. At the completion of the trial, each patient was asked to rank the three phases in descending order of preference.

**Exercise Testing**

Exercise testing was performed at $45^\circ$ to the horizontal on an exercise table attached to an electronically braked bicycle ergometer. During exercise, a 12-lead ECG, blood pressure measured by sphygmomanometer and symptoms were recorded every minute.

After the 2-week run-in period, when patients were taking placebo only, a baseline symptom-limited exercise test was performed (fig. 1) to identify two work loads for subsequent exercise radionuclide ventriculography. After each treatment phase, all patients underwent two exercise tests in the fasting state 3 hours after the last dose of medication (fig. 1). Short-acting nitrates were withheld for at least 8 hours before an exercise test. The first exercise test was symptom-limited (onset of chest pain or extreme fatigue or breathlessness). The second exercise test, performed 90 minutes later, was combined with gated equilibrium radionuclide ventriculography. The work loads for exercise radionuclide ventriculography were 50% (level 1) and 75% (level 2) of the highest work load achieved at the initial baseline exercise test. The work loads for each patient were identical for the three treatment phases. This exercise protocol has been reported.9,10 All exercise tests were done at the same time of the day, in the same position and on the same ergometer in an air-conditioned room with temperature kept at 20°C. ECGs at rest and during exercise were analyzed without knowledge of the patients’ clinical data.

**Radionuclide Ventriculography**

Multiple ECG-gated equilibrium radionuclide ventriculography was performed after the red cells were labeled in vivo with technetium-99m pertechnetate.11 Imaging was performed with the patient in a modified left anterior oblique position by an Ohio Nuclear gamma camera (Sigma 420) equipped with a 30°, slant-hole, high-sensitivity collimator12 and interfaced to a PDP 11 computer. The same collimator and camera angles were used for each patient during subsequent studies. Counts were collected for 6 minutes at rest and for the last 2 minutes of each 3-minute stage during exercise. An outline of the cardiac chambers was generated by a computer algorithm.13 Throughout all 24 frames, a variable region of interest was used to determine the changing count rate within the left ventricle. A computer-assigned background region two pixels from the end-systolic region around the apex and the lateral wall was used to correct for noncardiac activity. The left ventricular ejection fraction (EF) was then calculated from the time-activity curve using background-corrected end-diastolic and end-systolic counts. All radionuclide studies were analyzed by two independent, experienced operators without knowledge of the clinical data. Radionuclide measurement of EF using a variable region of interest in our laboratory correlates well with EF determined by single-plane right anterior oblique contrast ventriculography ($r = 0.91$). In 10 subjects studied on two different days, the mean difference in EF was $2 \pm 2\% \pm 3\%$ at rest and $3 \pm 3\%$ during exercise. The interobserver variability in EF at rest was $0.2 \pm 2\% \pm 3\%$ (n = 30) and in EF at peak exercise was $1.7 \pm 4\% \pm 3\%$ (n = 30).

**Propranolol and Verapamil Assay**

Blood samples were drawn 10 minutes before the second exercise test with gated equilibrium radionuclide ventriculography. Plasma verapamil was measured by high-pressure liquid chromatography14 and plasma propranolol by liquid chromatography.15

**Statistical Analysis**

All data were analyzed by analysis of variance of a $3 \times 3$ Latin square with six replications, except for anginal frequency and exercise time to angina, for which the Wilcoxon signed-rank test was used. There

<table>
<thead>
<tr>
<th>2 WEEKS</th>
<th>3 WEEKS</th>
<th>3 WEEKS</th>
<th>3 WEEKS</th>
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<tbody>
<tr>
<td>RUN IN</td>
<td>OFF</td>
<td>PHASE I</td>
<td>PHASE II</td>
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<td>1</td>
<td>2,3</td>
<td>2,3</td>
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**Figure 1.** Study protocol. 1 = baseline symptom-limited exercise test off therapy; 2 = symptom-limited exercise test at the end of each treatment phase; 3 = exercise radionuclide ventriculography.
was no significant difference in the order in which the three treatments were prescribed for any of the variables analyzed. When a significant difference between the three treatments was present \( p < 0.05 \), the treatment sums of squares was partitioned into "between placebo and propranolol," "between placebo and verapamil" and "between propranolol and verapamil" to identify the source of the significant difference. The results are expressed as mean \( \pm \) SD.

**Results**

**Symptoms, Side Effects and Preference for Therapy**

The frequency of anginal attacks was significantly reduced when both active drugs were compared with placebo, but there was no difference between patients during propranolol or verapamil therapy (placebo, 10.3 \( \pm \) 11 attacks of angina in the last 2 weeks of each 3-week treatment phase; propranolol, 1.9 \( \pm \) 2.7 attacks, \( p < 0.01 \); verapamil, 1.9 \( \pm \) 2.7 attacks, \( p < 0.01 \)). Four patients complained of significant side effects while taking propranolol (tiredness, dyspnea, fatigue and nightmares). While taking verapamil, one patient complained of mild constipation and two patients had asymptomatic prolongation of the PR interval to 0.22 second. At the end of the trial, seven patients preferred verapamil, four preferred propranolol, none preferred placebo, and seven expressed no preference for any of the three phases of treatment.

**Symptom-limited Exercise (table 1)**

The patients exercised longer and achieved higher maximal work loads while receiving active therapy. With propranolol there was a marked reduction in rate-pressure product during symptom-limited exercise, but a higher external work load was achieved than with placebo. Although the rate-pressure product with verapamil was the same as with placebo, the total external work performed was significantly higher. The mean time to onset of angina during placebo therapy was 4.6 \( \pm \) 1.2 minutes. Only three patients had angina during propranolol therapy and seven patients during verapamil therapy. Among patients who had angina, the time to onset of angina was increased by 0.7 \( \pm \) 0.5 minutes (\( p < 0.05 \)) during propranolol therapy and by 2 \( \pm \) 1.4 minutes (\( p < 0.01 \)) during verapamil therapy.

All 18 patients had a positive exercise ECG while taking placebo, compared with only seven patients during propranolol therapy and 11 patients during verapamil therapy. Both propranolol and verapamil significantly prolonged the time to 1 mm of ST depression and reduced maximal ST depression.

**Exercise at Identical Work Load (fig. 2)**

Propranolol markedly reduced the rate-pressure product at rest and at each exercise work load compared with both placebo and verapamil. During verapamil therapy, the rate-pressure product showed a small but significant reduction at rest and during exercise at identical work loads compared with placebo. The reduction in rate-pressure product was due to a lower systolic blood pressure at rest and a lower heart rate response during exercise.

**Left Ventricular Function at Identical Work Load (fig. 3)**

There were no significant differences in left ventricular EF at rest during placebo (57 \( \pm \) 13%), propranolol (55 \( \pm \) 12%) or verapamil therapy (55 \( \pm \) 13%). While taking placebo, all 18 patients had angina and a positive exercise test during level 2 exercise. Twelve patients had a decrease in EF of 5% or more, six patients had a decrease less than 5% and none had an increase. The mean EF decreased to 51 \( \pm \) 13% (\( p < 0.01 \)) during exercise.

During propranolol therapy, only two patients had angina and a positive exercise test. Twelve patients had an increase in EF of 5% or more, only two patients had a decrease in EF of more than 5%, and four patients had no change or less than a 5% decrease in EF. Overall, the mean EF increased to 62 \( \pm \) 10% during exercise, which was significantly higher than the EF during placebo therapy at the same work load (\( p < 0.01 \)).

While taking verapamil, four of the 18 patients had angina and a positive exercise test. Fourteen patients had an increase of 5% or more in EF, three patients had a less than 5% decrease in EF and only one patient had

**Table 1. Variables During Symptom-limited Exercise in 18 Patients**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo (P)</th>
<th>Propranolol (P)</th>
<th>Verapamil (V)</th>
<th>( p ) values</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>140 ( \pm ) 21</td>
<td>101 ( \pm ) 10</td>
<td>136 ( \pm ) 16</td>
<td>( p &lt; 0.005 ) NS &lt; 0.005</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>195 ( \pm ) 23</td>
<td>161 ( \pm ) 24</td>
<td>190 ( \pm ) 25</td>
<td>&lt; 0.01 NS &lt; 0.01</td>
</tr>
<tr>
<td>RPP ( \times 10^2 ) (beats/min/ mm Hg)</td>
<td>277 ( \pm ) 65</td>
<td>164 ( \pm ) 37</td>
<td>264 ( \pm ) 58</td>
<td>&lt; 0.01 NS &lt; 0.01</td>
</tr>
<tr>
<td>Exercise time (min)</td>
<td>6.8 ( \pm ) 1.2</td>
<td>7.6 ( \pm ) 1.4</td>
<td>7.8 ( \pm ) 1.7</td>
<td>&lt; 0.01 &lt; 0.01 NS</td>
</tr>
<tr>
<td>( \Sigma W ) (W-min)</td>
<td>424 ( \pm ) 135</td>
<td>513 ( \pm ) 168</td>
<td>545 ( \pm ) 215</td>
<td>&lt; 0.01 &lt; 0.005 NS</td>
</tr>
<tr>
<td>Time to 1 mm ST depression (min)</td>
<td>4.5 ( \pm ) 1.3</td>
<td>7.4 ( \pm ) 1.4</td>
<td>6.6 ( \pm ) 1.9</td>
<td>&lt; 0.005 &lt; 0.005 NS</td>
</tr>
<tr>
<td>Max ST depression (mm)</td>
<td>-2.6 ( \pm ) 0.7</td>
<td>-0.05 ( \pm ) 0.7</td>
<td>-1.3 ( \pm ) 1.1</td>
<td>&lt; 0.005 &lt; 0.005 &lt; 0.01</td>
</tr>
</tbody>
</table>

Values are mean \( \pm \) SD.

Abbreviations: HR = heart rate; SBP = systolic blood pressure; RPP = rate-pressure product; Ex = exercise; \( \Sigma W \) = total work.
more than a 5% decrease in EF. The mean EF increased to 62 ± 13%, which was significantly higher than EF during placebo therapy at the same work load (p < 0.01).

Plasma Drug Levels
The mean plasma propranolol level was 340 ng/ml (range 83–654 ng/ml). The mean plasma verapamil level was 169 ng/ml (range 85–306 ng/ml). Blood samples were taken approximately 4 hours after the last dose of medication. The mean plasma propranolol level in the seven patients who had 1 mm or more of ST depression during exercise was not significantly different from that of the 11 patients who had no ST depression (340 ± 151 vs 338 ± 216 ng/ml). Similarly, the mean plasma verapamil level in the 11 patients who had 1 mm or more of ST depression during exercise was not significantly different from that of the seven patients who had no ST depression (155 ± 61 vs 192 ± 75 ng/ml). Neither plasma propranolol nor plasma verapamil levels correlated with double product, work performance or exercise-induced changes in left ventricular EF.

Discussion
This study showed that in patients with effort angina, propranolol and verapamil (320 mg/day) reduced the frequency of angina and improved exercise capacity and ventricular function.

When patients were taking propranolol, the rate-pressure product was markedly reduced both at rest and during exercise, which suggests that the increased exercise capacity was due to a reduction in myocardial oxygen demand. During verapamil therapy, the rate-pressure product was slightly lower at rest and at each work load than with placebo, but was the same at peak exercise. Although the clinical effects were similar, the difference in hemodynamic effects suggests different actions of each drug. The mechanism of action of verapamil is not known and requires further study.

The rate-pressure product has been used as an indirect clinical index of myocardial oxygen demand. Two other determinants of myocardial oxygen demand, contractility and ventricular volume, are not measured in the rate-pressure product and may explain why at peak exercise it was the same with verapamil and placebo, even though exercise capacity and anginal threshold were different.

Leon et al.17 showed that resting systolic blood pressure was unchanged after 48 hours of verapamil, 320 mg/day. In our study and that of Johnson et al.,18 resting systolic blood pressure was reduced, but verapamil had been given for more than 2 weeks.

Ventricular Function at Rest
Neither propranolol nor verapamil depressed left ventricular EF at rest. Experimental studies have shown that verapamil has a negative inotropic effect.19,20 Our data show that chronic oral verapamil therapy does not change resting EF, a finding that has been reported by others.21 As verapamil decreases systemic vascular resistance, any negative inotropic action could be masked by a reflex increase in contractility caused by peripheral vasodilatation. Propranolol did not change resting EF in the present study, in agreement with two recent studies of chronic oral propranolol.22,23 This contrasts with the negative inotropic effect of i.v. propranolol24,25 and suggests that chronic oral and acute i.v. propranolol may have different effects on left ventricular function.

Ventricular Function During Exercise
A major finding in the present study is that both propranolol and verapamil significantly improved left ventricular function during exercise. At level 2 exercise, when all patients taking placebo had angina and ischemic ST depression, the EF decreased or did not change. In contrast, during therapy with either propranolol or verapamil, when exercise-induced ische-
mia did not occur, left ventricular function improved overall. In patients who had angina and ST depression at level 2 exercise despite drug therapy, EF decreased. This occurred in two patients during both the propranolol and verapamil phases and in another two patients during the verapamil phase. This suggests that the increased EF during exercise in the majority of patients in this study is due to the amelioration of exercise-induced ischemia by these drugs. Most of our patients had a normal EF at rest, but two patients had EFs of 40% and 28%. In these two patients, neither propranolol nor verapamil altered the EF at rest, but during exercise, EF increased in both patients.

The degree of β blockade was not directly assessed in our study, but a mean plasma level of 340 ng/ml (range 83–654 ng/ml) would have produced a high level of β blockade in all our patients, as shown by the substantial reduction in exercise-induced tachycardia. This high degree of β blockade is probably why the propranolol level did not correlate with exercise performance. There are no data on verapamil dose response in patients with effort angina. The mean level of 169 ng/ml (range 85–306 ng/ml) in this study has been shown to be adequate to control patients with coronary artery spasm who responded to verapamil. Clinical and practical constraints make dose-response curves difficult to obtain when comparing different drugs in the treatment of angina. Leon et al. studied two doses of oral verapamil (320 mg/day and 480 mg/day) each given for 48 hours and found that the higher dose was more effective in preventing exercise-induced angina. In our study, a higher dose of verapamil may have further improved exercise capacity, but 320 mg/day improved patients with exercise-induced angina by the same amount as propranolol, 320 mg/day. If a preliminary dose-ranging study had determined the dose of each drug, one drug may have been more effective than the other.

The results obtained using a relatively high fixed dose of propranolol and verapamil show they both increase exercise capacity, decrease anginal frequency, do not depress left ventricular ejection fraction at rest and improve it during exercise. Verapamil, 320 mg/day, is an effective primary therapy for patients with effort angina and is a satisfactory alternative to propranolol in patients in whom β blockade is undesirable or contraindicated.

**References**

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Effects of a Calcium-channel Antagonist on Large and Small Coronary Arteries in Conscious Dogs

STEPHEN F. VATNER, M.D., AND THOMAS H. HINTZE, PH.D.

SUMMARY The effects of i.v. nifedipine, 20 μg/kg, on left ventricular (LV) pressure, dp/dt, aortic pressure, heart rate, LV diameters, cardiac output, coronary blood flow and left circumflex coronary arterial diameter, and calculations of late diastolic coronary and total peripheral resistances and left circumflex coronary cross-sectional area were examined in 11 conscious dogs. In dogs with spontaneous rhythm, nifedipine induced an early, transient response characterized by hypotension and peak increases in coronary blood flow and decreases in total peripheral and late diastolic coronary vascular resistances. The peak effects on large coronary arteries were observed 2–5 minutes later, when mean arterial pressure was only 82 ± 1.6 mm Hg below control and LV end-diastolic pressure and diameter were not significantly different from control. LV dp/dt was elevated by 7.1 ± 1.1%, heart rate was elevated by 25 ± 3.3 beats/min, and cardiac output remained elevated by 54 ± 7.4%. At this time, coronary cross-sectional area was elevated by 26 ± 3.0%, late diastolic coronary vascular resistance was reduced by 50 ± 2.7%, and total peripheral resistance was 40 ± 3.8% below control. The coronary sinus oxygen content was elevated by 3.4 ± 0.8 vol% and the arteriovenous oxygen difference fell by 3.5 ± 0.8 vol%. After β-adrenergic blockade with propranolol and with heart rate constant or varying, the increases in coronary cross-sectional area and decreases in late diastolic coronary vascular resistance induced by nifedipine were still observed, but were significantly smaller (p < 0.01). Thus, nifedipine dilates both large coronary arteries and coronary resistance vessels, effects that could be attributed in part to β-adrenergic mechanisms. Nifedipine also exerts potent effects on coronary and peripheral arterial vessels, but has little effect on preload.

ANTAGONISTS of slow-channel calcium exchange are now widely used to treat coronary vasospasm and typical angina pectoris. These drugs dilate peripheral vessels and coronary resistance vessels under normal conditions and enhance blood flow to ischemic myocardium during coronary artery occlusion. In patients with coronary artery disease, calcium antagonists increase coronary blood flow. Despite the mass of recent data on the action of these drugs, several questions about the effects of calcium antagonists on the coronary circulation have not been resolved. These questions relate to: (1) the specificity of these drugs for small or large coronary arteries, (2) whether the dilation of coronary vessels involves β-adrenergic mechanisms, (3) whether the dilation of coronary vessels is independent of changes in heart rate and myocardial contractility, (4) the relationship of the potency for dilation of coronary vessels to that of the systemic circulation, and (5) the extent to which the drugs re-

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