Comparative effects of propranolol and verapamil alone and in combination on left ventricular function and volumes in patients with chronic exertional angina: a double-blind, placebo-controlled, randomized, crossover study with radionuclide ventriculography

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With the technical assistance of Paul D. Purves, R.T.N.M.

ABSTRACT With the use of equilibrium radionuclide ventriculography the effects on left ventricular (LV) function of 160 mg oral propranolol daily and 360 mg verapamil daily alone and in combination were compared in 18 patients with chronic exertional angina. A randomized, double-blind, placebo-controlled, crossover protocol was used. The reduction in exercise rate-pressure product induced by the combination (118 ± 28 mm Hg/min) was significantly greater (p < .05) than that by propranolol (135 ± 27 mm Hg/min) or verapamil alone (163 ± 28 mm Hg/min). In patients at rest, neither single nor combined therapy altered global or regional left ventricular ejection fractions (EFs). Verapamil, but not propranolol, increased (p < .05) cardiac volumes of resting subjects; used in combination, no further increase in LV volume occurred. With placebo, exercise global EF did not decrease from the level at rest and therefore no drug effect could be demonstrated for this parameter of LV function. By an evaluation of normalized regional EF measurements the combination was shown to reduce exercise-induced hypokinesis (placebo 52 ± 20%, combination 61 ± 23%; p < .01). No significant improvement was noted with propranolol or verapamil alone; only the combination prevented a significant increase in end-systolic and end-diastolic volumes during exercise. Thus, propranolol and verapamil, used alone in moderate doses, exert no beneficial effect on exercise LV function as measured by EF and volume changes, and resting function deteriorates slightly with verapamil. Compared with single-drug therapy, the combination causes no further change in LV function of resting subjects and improves exercise function. This improvement was most likely due to a reduction in myocardial oxygen demand.

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COMBINATION THERAPY with β-adrenergic-receptor antagonists and nitrates is a well-established part of the treatment of chronic exertional angina. Recently, reports have shown that calcium-channel antagonists such as verapamil have antianginal properties comparable to those of propranolol.1–4 Moreover, in selected patients, the combination of propranolol and verapamil may provide an antianginal effect superior to either drug alone.4, 9, 10 The antianginal properties of propranolol differ in some respects from those of verapamil, providing a rationale for the use of combined therapy. Propranolol reduces the heart rate and blood pressure response both in patients at rest and during maximal exercise, thus decreasing myocardial oxygen demand. While verapamil reduces heart rate and blood pressure during submaximal exercise,4 the rate-pressure product at maximal exercise is usually similar or only slightly lower than that observed during the control period.1–8 Despite this finding, clinical improvement with a reduction in the incidence of angina is often evident at maximal exercise, suggesting that ver-
apamil has another mechanism of action that is responsible for its beneficial effect in patients with exertional angina. Both a coronary artery vasodilatory action\textsuperscript{11} and improvement in diastolic filling properties have been suggested.\textsuperscript{12} Unfortunately, since both drugs exert significant negative inotropic and chronotropic effects, concern has arisen regarding the adverse effects of $\beta$-blockade and calcium-antagonist combination therapy.\textsuperscript{13, 14}

At the present time, limited data are available concerning left ventricular performance, and in particular left ventricular volume changes associated with combined oral $\beta$-receptor blockade and calcium-antagonist therapy over a prolonged period. Data obtained from short-term invasive studies have revealed additive cardio depressant effects.\textsuperscript{15, 16} Although the significance of these changes remains controversial, it is generally accepted that caution should be exercised when the combination is used in the presence of left ventricular dysfunction. Accordingly, our study was undertaken to determine what, if any, detrimental effects therapy with the combination of oral propranolol and verapamil had on the left ventricular function of resting and exercising subjects. Several radionuclide variables were examined to help clarify the mechanism by which these drugs exert their actions.

**Methods**

**Patient population.** Nineteen men and one woman, 38 to 73 years old (mean 57), with Canadian Cardiovascular Society functional class II or III stable exertional angina were studied. While off all antianginal medication, patients experienced two or more episodes of exertional angina per week and during treadmill exercise they had an ischemic electrocardiographic response (horizontal or downsloping ST segment depression of at least 1 mm). All patients had to terminate treadmill exercise due to angina. Patients were in sinus rhythm with a PR interval $\leq 0.20$ sec in duration and a QRS complex width of $\leq 0.12$ sec. Six patients had a history of a remote myocardial infarction ($\geq 6$ months). Fourteen patients had undergone coronary angiography within 1 year of the study and all had significant coronary artery disease (defined as $\geq 50\%$ diameter vessel narrowing). Three, four, and seven patients had one-, two-, and three-vessel coronary artery disease, respectively. Two patients previously underwent coronary artery bypass surgery. In no patient was there clinical evidence of hypertension, valvular heart disease, chronic obstructive lung disease, or heart failure. Three patients had radionuclide evidence of left ventricular dysfunction with reduced ejection fractions of 22\%, 28\%, and 48\%. Patients from the outpatient department and in-hospital population were assessed in a consecutive manner and those meeting entry criteria were included in the study.

**Study design (figure 1).** Following 1 week of gradual weaning from previous medication, patients entered a 5 to 7 day open control period during which eligibility for study entry was determined and preliminary exercise tests were performed. For the double-blind, crossover portion of the study, four 1 month treatment periods were randomly allocated (table of random numbers) by the pharmacy department to each of the 20 patients with

<table>
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<tr>
<th>RANDOMIZE</th>
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<tr>
<td>1 wk</td>
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<td><strong>CONTROL</strong></td>
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**FIGURE 1.** The study design consisted of a 1 week open control period to assess study eligibility followed by four randomized 4 week periods of treatment assigned in a double-blind, crossover fashion.

A double-dummy technique. The four treatment periods consisted of the following: placebo plus placebo, propranolol plus verapamil placebo, propranolol placebo plus verapamil, and propranolol plus verapamil.\textsuperscript{4} Singly or in combination, propranolol was administered in a dosage of 40 mg four times a day and verapamil in a dosage of 120 mg three times a day. At the end of each treatment period patients underwent exercise testing followed by a 1 week down-titration of both drug dosages before crossing over to the next treatment. Drug administration was begun without dose titration. In all but one patient, cardiac medication unrelated to the study drugs was discontinued; in the one patient who remained on oral nitrates this drug was discontinued 24 hr before each exercise test. Patients were assessed 2 weeks after beginning each new treatment. Upon completion of each treatment period, a full history and physical examination were obtained, diaries were reviewed, and adverse effects and pill count results were recorded. Care was taken to ensure that patients ingested their last dose of medication approximately 2 hr before exercise. Each patient exercised on all occasions at the same time of day.

**Radionuclide ventriculography.** Electrocardiographic multigated equilibrium radionuclide ventriculography was performed with the patient in the supine position to assess left ventricular function and volume at rest and during submaximal and maximal exercise. After in vivo labeling of red blood cells with 20 mCi of technetium-99m pertechnetate, cardiac scintigraphy was performed with patients in the left anterior oblique position that best isolated the left ventricle. A study to obtain resting values was performed after the patient’s legs were elevated for at least 2 min. All images were collected for 2 min with a conventional Anger scintillation camera equipped with a high-sensitivity parallel-hole collimator interfaced to a dedicated medical computer system.\textsuperscript{17} Data were collected in a continuous electrocardiographic synchronized mode with 16 frames spanning the cardiac cycle. Approximately 180,000 to 200,000 counts/frame were obtained with this method. Patients began supine exercise at an initial workload of 25 W and this was increased successively by 25 W every 3 min until exercise was terminated due to patients’ symptoms. Images were acquired during the last 2 min of each exercise stage.

Data were analyzed with a mobile medical computer (Ohio Nuclear Model 550). To calculate global left ventricular ejection fraction, a background region of interest was drawn manually along the image of the inferolateral left ventricular free wall in the end-systolic and end-diastole (previously identified from the left ventricular time-activity curve) with the use of an endless-loop

\*Verapamil and placebo tablets were supplied by G. D. Searle & Co. of Canada Limited, Oakville, Ontario.
cine display to improve edge detection. This was done on three separate occasions and an average of the three count measurements for each of the two frames was used to calculate ejection fraction. As determined by this method in our laboratory, resting radionuclide left ventricular ejection fraction correlated closely with that obtained by biplane contrast angiography in 28 patients ($r = .92$; SEE = 7.6 ejection fraction percentage points).

Based on principles previously described,18 operator-defined radii were placed to derive absolute septal, apical, and lateral regional ejection fractions while excluding the aortic and mitral valve planes. Each regional ejection fraction measurement was then normalized by dividing it by the mean normal ejection fraction for that region, which was previously determined in 23 healthy subjects. Normalized values that were <$80\%$ of the mean normal value were considered to be hypokinetic while values $>80\%$ were considered to be normokinetic. Left ventricular segments were assessed visually and classified as normal, hypokinetic, akinetic, or dyskinetic (scored 0, 1, 2, and 3, respectively).

Left ventricular volumes were calculated by a count-based, nongeometric method without individual attenuation correction that was modified from that described by others.19,20 Background-corrected end-diastolic and end-systolic regions of interest were generated as described for the calculation of global ejection fraction. End-systolic and end-diastolic volumes were derived from the count measurements and normalized for counts per milliliter of peripheral venous blood. As in an earlier study,21 we demonstrated in our preliminary experiments a significant increase in radioactive-tracer concentration during successive stages of exercise. This necessitated withdrawal of 3 ml of peripheral venous blood from patients at rest and midway through the exercise period. By this method, the correlation coefficient for contrast and radionuclide ventriculography in 28 previously studied patients was .95 (SEE = 22.5 ml) for end-diastolic volume and .97 (SEE = 17.2 ml) for end-systolic volume.

Twenty-three normal subjects who were a mean 55 years old (range 41 to 65) volunteered to undergo radionuclide ventriculography. No subject had a history of cardiovascular disease or previous cardiac catheterization and all had normal physical examination results, electrocardiograms, chest x-rays, and thallium-201 treadmill exercise test results. These normal values describing supine resting and exercise left ventricular function are listed in table 1. Significant changes occurred in radionuclide-derived left ventricular ejection fractions and volumes (p < .001 and p < .01, respectively) from rest to exercise. Radionuclide ventriculographic data for normal and study subjects were analyzed in a blinded fashion.

**Statistical analysis.** Two-way analysis of variance was used to determine the significance of change in mean heart rate, blood pressure, and left ventricular ejection fraction and volumes during treatment periods. If significance was detected, Tukey’s multiple comparison test was used to compare means. If the distribution of measurements appeared skewed, the Wilcoxon signed-rank test was used. To analyze change from rest to exercise the paired t test was used. Regression analyses were performed to derive the correlation coefficient, slope, intercept, and SEE in the conversion of radionuclide volumes to absolute volumes. Syringe counts obtained during staged exercise were analyzed by regression analysis with repeated measurements.22 Exercise stage was used as the predictor variable. By two-way analysis of variance intraobserver, interobserver, and interstudy variances for determination of left ventricular ejection fraction and volume were calculated with data from 25 previous studies in resting patients with coronary artery disease. Variance was defined as the pooled error due to observational differences and

| TABLE 1
Indexes of left ventricular function and volumes in 23 normal subjects |
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<tbody>
<tr>
<td></td>
<td>At rest</td>
<td>During supine exercise</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>65 ± 11</td>
<td>129 ± 20</td>
</tr>
<tr>
<td>Global EF (%)</td>
<td>68 ± 5</td>
<td>75 ± 6</td>
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<tr>
<td>Septal EF (%)</td>
<td>46 ± 7</td>
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<td>Apical EF (%)</td>
<td>58 ± 11</td>
<td>72 ± 13</td>
</tr>
<tr>
<td>Lateral EF (%)</td>
<td>71 ± 12</td>
<td>79 ± 12</td>
</tr>
<tr>
<td>EDVI (ml/m²)</td>
<td>93 ± 24</td>
<td>100 ± 25</td>
</tr>
<tr>
<td>ESVI (ml/m²)</td>
<td>31 ± 9</td>
<td>27 ± 10</td>
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<td>PSP/ESVI ratio</td>
<td>3.9 ± 2.1</td>
<td>7.6 ± 3.9</td>
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<td>SVI (ml/m²)</td>
<td>61 ± 16</td>
<td>73 ± 18</td>
</tr>
<tr>
<td>CI (l/m²/min)</td>
<td>3.9 ± 0.8</td>
<td>9.4 ± 2.1</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

EF = ejection fraction; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; PSP = peak systolic pressure; SVI = stroke volume index; CI = cardiac index.

the residual error,23,24 and values were expressed as ±2 SD. By a previously described method,24 interstudy variance was determined by comparing results of two consecutive resting studies in which similar techniques and data analysis were used. The largest of the three variance values was used in defining a significant change induced by an intervention. Frequency differences were compared with the McNemar test. A p value of ≤.05 was considered significant.

**Results**

**Intraobserver, interobserver, and interstudy variance.** Analysis of pooled variance showed that for left ventricular ejection fraction a change of 5% (absolute value) or more after any intervention was significant at the 5% level. For septal, apical, and lateral ejection fraction, changes of 7%, 7%, and 9%, respectively, were significant. Change in end-distolic and end-systolic volume indices of 10 and 7 ml/m² or more, respectively, were significant at the 5% level.

**Clinical response and adverse drug effects.** Of the 20 patients who entered the study, two withdrew after randomization to therapy. One patient developed symptomatic bradycardia while taking the combination and the other developed a skin rash while taking verapamil. The most common side effects were fatigue with propranolol (two patients) and constipation with verapamil (five patients); these same symptoms usually recur when the drugs were taken in combination. Three patients developed evidence of heart failure characterized by the presence of symptoms, mainly dyspnea, or pulmonary vascular congestion on chest x-ray during combination therapy. One of these patients also complained of dyspnea while on propranolol. Of these three patients, two had significant decreases in their resting ejection fractions (from 48% to 42% and from 65% to 59%). The patient who developed heart
failure on both propranolol alone and the combination had a rise in resting ejection fraction from 22% with placebo to 29% with propranolol and to 27% with the combination. End-systolic and end-diastolic volumes increased significantly in all four instances, but the increases were no greater than those noted in patients who did not complain of dyspnea. Three patients reported orthostatic dizziness during combination therapy. Four patients developed asymptomatic first-degree atrioventricular block while on the combination. Thirteen patients experienced angina during supine exercise after placebo and propranolol, and 11 and nine had angina after verapamil and the combination, respectively. Review of patient diaries revealed slight but insignificant reductions in the number of angina attacks and in nitroglycerin consumption with all treatments.

Heart rate, blood pressure, and electrocardiographic changes (table 2, figure 2). A significant reduction in the supine resting heart rate occurred with both propranolol (p < .001) and verapamil (p < .05) compared with placebo; this reduction was greater with propranolol (p < .05) and the combination (p < .01) than with verapamil. Although combination therapy decreased resting heart rate more than did propranolol, this difference was not significant. Significant reductions in supine resting systolic and diastolic blood pressures (p < .01 and p < .05, respectively) were observed during all treatment periods. Resting rate-pressure product was diminished (p < .001) by propranolol and the combination and, to a lesser extent (p < .01), by verapamil. During maximal exercise, heart rate was reduced by both propranolol (p < .001) and the combination (p < .01) when compared with placebo; no significant reduction occurred after verapamil. Exercise heart rate was diminished more by the combination than by propranolol (p < .05) and verapamil (p < .01) and exercise systolic blood pressure was reduced (p < .01) after propranolol and the combination but not after verapamil. Exercise rate-pressure product was decreased by propranolol (p < .001), verapamil (p < .05), and the combination (p < .001) when compared with placebo. Compared with verapamil or propranolol alone, the combination reduced rate-pressure product more (p < .001 and p < .05, respectively). To investigate the mechanism by which the combination exerted its beneficial effect on exercise-induced ischemia of the myocardium, rate-pressure product during the first stage of placebo exercise was determined and compared with that at maximal exercise during administration of the combination. The rate-pressure product at submaximal exercise with placebo was not significantly different from that observed during maximal exercise with the combination (placebo 125 ± 21 mm Hg/min, combination 118 ± 28 mm Hg/min). Exercise-induced ST segment depression was reduced from that after placebo (1.9 ± 1.4 mm) by verapamil (1.5 ± 1.0 mm) and the combination (1.1 ± 1.0 mm) but not by propranolol (1.7 ± 1.2 mm).

Global ejection fraction (table 2, figure 3). Resting global ejection fraction was not changed by any of the treatments. The slight reduction (59% to 55%) observed with verapamil therapy was not significant. During the control period, before randomization to

### Table 2
Effect of propranolol and verapamil alone and in combination on supine heart rate, blood pressure, rate-pressure product, left ventricular global ejection fraction, left ventricular volumes, and cardiac index

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Propranolol</th>
<th>Verapamil</th>
<th>Combination</th>
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<tr>
<td></td>
<td>R Ex</td>
<td>R Ex</td>
<td>R Ex</td>
<td>R Ex</td>
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<tr>
<td>HR (bpm)</td>
<td>70 ± 15</td>
<td>109 ± 15</td>
<td>60 ± 10</td>
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<td></td>
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<td>67 ± 9</td>
<td>103 ± 15</td>
<td>55 ± 7</td>
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<tr>
<td>SBP (mm Hg)</td>
<td>141 ± 23</td>
<td>166 ± 25</td>
<td>130 ± 21*</td>
<td>151 ± 21*</td>
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<td></td>
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<td>127 ± 16*</td>
<td>158 ± 17</td>
<td>126 ± 15*</td>
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<td></td>
<td></td>
<td>81 ± 8*</td>
<td>89 ± 10</td>
<td>78 ± 8*</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>86 ± 10</td>
<td>90 ± 13</td>
<td>81 ± 11*</td>
<td>88 ± 13*</td>
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<td></td>
<td></td>
<td>85 ± 13*</td>
<td>163 ± 28*</td>
<td>69 ± 10*</td>
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<td></td>
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<td>55 ± 14</td>
<td>54 ± 15</td>
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<td>54 ± 15</td>
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<td>RPP (beats-mm Hg/min)</td>
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<td>182 ± 38</td>
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<td>55 ± 14</td>
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<td>105 ± 30*</td>
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<td></td>
<td></td>
<td>48 ± 25*</td>
<td>56 ± 26</td>
<td>47 ± 22*</td>
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<tr>
<td>EDVI (ml/m²)</td>
<td>93 ± 25</td>
<td>109 ± 26</td>
<td>103 ± 31</td>
<td>118 ± 30</td>
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<tr>
<td></td>
<td></td>
<td>3.2 ± 1.2*</td>
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<td>3.6 ± 1.0</td>
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<tr>
<td>ESVI (ml/m²)</td>
<td>40 ± 24</td>
<td>52 ± 26</td>
<td>45 ± 27</td>
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<td></td>
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<td>48 ± 25*</td>
<td>56 ± 26</td>
<td>47 ± 22*</td>
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<tr>
<td>SVI (ml/m²)</td>
<td>52 ± 16</td>
<td>56 ± 12</td>
<td>58 ± 14</td>
<td>63 ± 13</td>
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<td></td>
<td></td>
<td>57 ± 20</td>
<td>61 ± 17</td>
<td>63 ± 17*</td>
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<tr>
<td>CI (l/min/m²)</td>
<td>3.7 ± 0.9</td>
<td>5.9 ± 1.5</td>
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<tr>
<td></td>
<td></td>
<td>3.6 ± 1.0</td>
<td>5.9 ± 1.6</td>
<td>3.3 ± 0.6*</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

R = rest; Ex = exercise; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; RPP = rate-pressure product; EF = ejection fraction; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; SVI = stroke volume index; CI = cardiac index; PSP = peak systolic pressure.

\*p < .05; \*p < .01; \*p < .001 vs placebo.
FIGURE 2. Effects of therapy on supine heart rate, systolic blood pressure, diastolic blood pressure, and rate-pressure product (× 10⁻²). The combination reduced exercise rate-pressure product significantly (p < .05) compared with propranolol. Values are mean values. PL = placebo; P = propranolol; V = verapamil; R = rest; Ex = exercise. *p < .05; †p < .01; ‡p < .001 vs placebo.

treatment, ejection fraction decreased significantly (p < .01) from rest (56 ± 15%) to exercise (49 ± 16%), but during the placebo period the decrease in ejection fraction from rest to exercise was not significant. Thus, drug effect on this parameter of exercise left ventricular function could not be shown. Assessment of individual patient response showed that a significant decrease in exercise ejection fraction occurred in seven patients on placebo, 10 on propranolol, five on verapamil, and in 11 on the combination.

Regional ejection fraction and wall motion score (table 3). There was no significant change in resting regional ejection fraction during any of the treatment periods. With exercise, absolute septal, apical, and lateral regional ejection fractions decreased slightly in patients taking placebo, but only the reduction in apical ejection fraction was significant (51 ± 17% to 46 ± 19%, p < .05). This reduction was prevented by verapamil (49 ± 15% to 46 ± 18%) and the combination (52 ± 14% to 48 ± 17%), but not by propranolol (54 ± 15%)

FIGURE 3. Effects of therapy on group (mean ± SD) and individual supine global left ventricular ejection fraction values. Compared with after placebo, mean resting and exercise ejection fraction remained unchanged during all treatment periods. ns = not significant versus rest. Abbreviations are as in figure 2.
to 46 ± 16%). After normalization, hypokinetic and normokinetic segments were isolated. Compared with placebo, both propranolol and the combination increased (p < .05) resting hypokinetic segment function. Verapamil demonstrated no effect. During submaximal exercise with placebo, hypokinetic segment function was significantly improved compared with at maximal exercise (submaximal 60 ± 19%, maximal 52 ± 20%; p < .05). This submaximal exercise value was not different from that after propranolol or the combination but was greater (p < .05) than that after verapamil. During maximal exercise only combined therapy improved hypokinetic segment function (p < .01). Normokinetic segment function was reduced during exercise by both verapamil and the combination (p < .05 and p < .01, respectively). Visual assessment of regional wall motion showed no change in resting wall motion score with any treatment and no significant change occurred from rest to exercise with placebo.

**Left ventricular volume (table 2, figures 4 and 5).** Resting end-diastolic volume increased significantly from that in patients taking placebo after verapamil (p < .05) and after the combination (p < .01). Likewise, resting end-systolic volume increased with verapamil (p < .05) and the combination (p < .05) when compared with after placebo. The changes in left ventricular volume induced by propranolol were not significant. Compared with after placebo, the ratio of peak systolic pressure to end-systolic volume index (PSP/ESVI), a noninvasive measure of the left ventricular pressure/volume relationship, was diminished (p < .05) at rest by verapamil and the combination. Exercise end-systolic and end-diastolic volumes and PSP/ESVI did not change significantly with any therapy when compared with the placebo exercise values. However, the highly significant increase (p < .001) in end-systolic volume that occurred from rest to exercise in patients on placebo was reduced slightly by propranolol and verapamil and prevented by the combination. The marked increase (p < .001) that occurred in exercise end-diastolic volume in patients on placebo was prevented by the combination only. No significant changes occurred in the exercise PSP/ESVI ratios from

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**TABLE 3**

Effect of therapy on normalized left ventricular segments

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<tr>
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<th>Placebo</th>
<th>Propranolol</th>
<th>Verapamil</th>
<th>Combination</th>
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<tbody>
<tr>
<td>At rest (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokinetic segments (n = 17)</td>
<td>57 ± 24</td>
<td>73 ± 28&lt;sup&gt;a&lt;/sup&gt;</td>
<td>60 ± 34</td>
<td>70 ± 33&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Normokinetic segments (n = 37)</td>
<td>101 ± 17</td>
<td>102 ± 20</td>
<td>99 ± 15</td>
<td>97 ± 17</td>
</tr>
<tr>
<td>During exercise (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokinetic segments (n = 36)</td>
<td>52 ± 20</td>
<td>57 ± 20</td>
<td>55 ± 21</td>
<td>61 ± 23&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Normokinetic segments (n = 18)</td>
<td>96 ± 12</td>
<td>91 ± 13</td>
<td>87 ± 14&lt;sup&gt;a&lt;/sup&gt;</td>
<td>83 ± 12&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

<sup>a</sup>p < .05; <sup>b</sup>p < .01 vs placebo.
rest to exercise with placebo or any of the treatments. Resting stroke volume increased only with the combination (p < .05). Exercise stroke volume did not significantly increase during any treatment period when compared with placebo or resting values. Rest and exercise cardiac indices were depressed (p < .05 and p < .01, respectively) only by the combination. All treatment periods were associated with a significant (p < .001) increase in cardiac index from rest to exercise. Although no patients had clinically significant mitral regurgitation at rest, transient mitral regurgitation may have developed in some patients at peak exercise. Thus, the derived cardiac indices represent the total left ventricular flow and not necessarily forward flow alone.

Discussion

Changes in resting values. Neither propranolol nor verapamil caused a significant change in resting global left ventricular ejection fraction. Importantly, the combination of these drugs did not result in a reduction of this parameter either. The lack of change in ejection fraction that we observed is in agreement with the findings of other investigators,2, 5, 10, 12, 24–27 although in one study a slight reduction was demonstrated after high-dose verapamil.12 Even in the presence of impaired left ventricular function, global ejection fraction may not change after oral propranolol or verapamil.27–30

Observation of changes in cardiac volumes, particularly end-systolic volume and the PSP/ESVI ratio, provides a useful method of assessing the effects of pharmacologic interventions on left ventricular function.31–33 In the present study, propranolol did not significantly alter these parameters. Although limited data are available, previous reports on the effects of oral propranolol on resting left ventricular volumes have varied. Some investigators have found a slight increase in end-diastolic volume,34, 35 while others have found no change.30, 36, 37 Similarly, a variable response for end-systolic volume has been noted.30, 38 Studies in which intravenous β-receptor-blocking drugs have been used have shown a decrease in ejection fraction, stroke volume, and cardiac output with an increase in end-systolic and end-diastolic volumes.38–41 Whether the effect of oral propranolol on left ventricular volume is due to a slowing of heart rate or a direct myocardial depressant action has not been firmly established.36 Verapamil caused a reduction in myocardial contractility, as shown by an increase in end-systolic volume and a decrease in the PSP/ESVI ratio. Previous studies of the effect of verapamil on the intact human cardio-vascular system have produced conflicting data.42, 43 Although isolated cardiac muscle and animal studies have clearly shown the myocardial depressant effect of verapamil,44, 45 it has been demonstrated infrequently in the clinical setting. In particular, a consistent effect on left ventricular ejection fraction and volume has not been shown. Klein et al.46 showed how knowledge of the timing of data acquisition and of baseline left ventricular function is vital to the interpretation of results after administration of intravenous verapamil. Immediately after administration of verapamil, left ventricular function was depressed and ejection fraction reduced. This was followed quickly by the development of supernormal function, as demonstrated by a rise in ejection fraction above baseline and a decrease in volume below baseline; these changes were presumably due to a reflex compensatory response. Within 8 to 10 min after the bolus of verapamil these variables returned to baseline.

Our observation that combination therapy with moderate-dose propranolol and verapamil was unassociated with an additive myocardial depressant effect was in keeping with results of other investigations.9, 10, 47 In contrast, after administering single-dose oral verapamil to patients receiving high-dose propranolol, Packer et al.48 observed a detrimental hemodynamic effect of the combination.

Verapamil and propranolol may exert either no effect or a detrimental effect on resting hypokinetic segment function.30, 48, 49 Using normalized regional ejection fraction, our study showed that both propranolol and the combination improved function of hypokinetic segments in resting patients. Our results differ from those of previous studies due to our use of radionuclide-derived, count-based regional ejection fractions. The dimensional assessment by this method may provide more information than visually scored wall motion observed from a cine display. Preload did not appear to play a role in this response and it is likely that propranolol and the combination favorably influenced mild-to-moderately impaired left ventricular segment function.

Changes in exercise values. Most investigations examining the effects of pharmacologic interventions on left ventricular function depend on the observation of changes in global ejection fraction from rest to exercise.3, 5, 12, 25–27 In these studies, exercise ejection fraction during therapy is usually not significantly different from the control exercise value so that the change from control is not easily recorded. Consequently, in observing changes from rest to exercise, erroneous conclusions may be drawn. A fall in ejection fraction may
be prevented solely by depression of resting ejection fraction, in which case there is no beneficial effect on exercise function. By normalizing regional ejection fraction measurements and isolating hypokinetic segments, we were able to observe the actions of various pharmacologic interventions on exercise-induced ischemia in myocardial segments. Changes in left ventricular function could be easily compared with control measurements. In this study, a significant improvement in exercise-induced hypokinesis occurred only with the combination therapy and this beneficial effect was associated with a significant reduction in rate-pressure product compared with after propranolol alone. In addition, at an equivalent rate-pressure product hypokinetic segment function was similar with placebo and the combination. This finding supported work by Leon et al.,\textsuperscript{4} who suggested that the primary mechanism of action of the combination was to reduce myocardial oxygen demand.

Exercise-induced ischemia, in addition to depressing exercise global ejection fraction, may also cause an increase in end-systolic volume.\textsuperscript{50} Our study demonstrated a highly significant increase in end-systolic volume in patients taking placebo. Although this was limited to some extent by propranolol and verapamil, only the combination prevented a significant increase. This finding, together with the observed effect on exercise hypokinetic segments, clearly demonstrated the beneficial anti-ischemic properties of the combination.

The relationship between left ventricular ejection fraction and volumes and symptoms of heart failure has not been established. Calculation of these parameters in our study did not aid in identifying those patients who developed clinical evidence of drug-induced heart failure. Others have shown a direct correlation between radionuclide-derived end-diastolic volume and pulmonary capillary wedge pressure, suggesting that an increase in end-diastolic volume may be observed in the presence of drug-induced pulmonary edema.\textsuperscript{51} Although in our study end-systolic and end-diastolic volumes increased in all patients who became dyspneic, these changes were not significantly different from those noted in patients who did not develop dyspnea.

Our data demonstrated how loading conditions influence ejection fraction and that measurement of this variable only may not provide an adequate assessment of the effect of a pharmacologic intervention on left ventricular function. Ejection fraction, a measure of systolic function that is partly dependent on end-systolic volume,\textsuperscript{52} did not detect the significant increase in resting end-systolic volume caused by verapamil due to a concomitant increase in end-diastolic volume. Similarly, during exercise a highly significant increase in end-systolic volume occurred with placebo and single-drug therapy, and it occurred without a reduction in global ejection fraction. Thus, this parameter was not helpful in detecting the beneficial effect of the combination therapy on exercise left ventricular function. The failure to observe a significant decrease in exercise ejection fraction during placebo administration cannot be readily explained. A greater ischemic response would presumably increase end-systolic volume further, causing a reduction in ejection fraction. End-systolic volume may be a more sensitive indicator of ischemia and subsequent drug effect.

The effect of verapamil on normal exercise left ventricular function has not been previously described. By observing normokinetic segment function, our data would suggest that verapamil depresses normal exercise ventricular function. Also, assessment of normokinetic segment function permitted further understanding of the global ejection fraction response. For example, although the combination depressed exercise normokinetic segment function, exercise global ejection fraction did not fall below the exercise placebo value because of improvement in exercise-induced hypokinesis.

In conclusion, combination therapy with propranolol and verapamil in patients with exertional angina and normal or near-normal left ventricular function is not associated with worsening of resting systolic function when compared with single-drug therapy. Moreover, only the combination significantly improves exercise left ventricular function, and in doing so it is associated with an additional decrease in the rate-pressure product, which implies a reduction in myocardial oxygen demand. Although this combination therapy improves exercise left ventricular function it should be used with caution because of the potential for adverse effects.

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