Effects of Verapamil and Propranolol on Left Ventricular Systolic Function and Diastolic Filling in Patients with Coronary Artery Disease: Radionuclide Angiographic Studies at Rest and During Exercise

ROBERT O. BONOW, M.D., MARTIN B. LEON, M.D., DOUGLAS R. ROISING, M.D., KENNETH M. KENT, M.D., PH.D., LEWIS C. LIPSON, M.D., STEPHEN L. BACHARACH, PH.D., MICHAEL V. GREEN, M.S., STEPHEN E. EPSTEIN, M.D.

SUMMARY To determine the effects of verapamil on left ventricular (LV) systolic function and diastolic filling in patients with coronary artery disease (CAD), we performed gated radionuclide angiography at rest and during exercise in 16 symptomatic patients before and during oral verapamil therapy (480 mg/day). Twelve patients were also studied during oral propranolol (160–320 mg/day). LV ejection fraction at rest was normal in 13 patients, but abnormal diastolic filling at rest, defined as peak filling rate (PFR) < 2.5 end-diastolic volumes (EDV)/sec or time to PFR > 180 msec, was present in 15. During verapamil, resting ejection fraction decreased (control 50 ± 10% [± SD], verapamil 45 ± 12%, p < 0.005), but resting diastolic filling improved: PFR increased (control 1.9 ± 0.6 EDV/sec, verapamil 2.3 ± 0.9 EDV/sec, p < 0.005) and time to PFR decreased (control 185 ± 38 msec, verapamil 161 ± 27 msec, p < 0.05). Exercise ejection fraction did not change during verapamil (control 42 ± 13%, verapamil 43 ± 12%, NS), but exercise PFR increased (control 3.1 ± 0.9 EDV/sec, verapamil 3.6 ± 1.1 EDV/sec, p < 0.05) and exercise time to PFR decreased (control 108 ± 30 msec, verapamil 91 ± 17 msec, p < 0.05). In contrast, propranolol did not alter ejection fraction, PFR, or time to PFR at rest or during exercise. Thus, LV ejection fraction is decreased by verapamil at rest but is unchanged during exercise. While LV systolic function is not improved by verapamil, LV diastolic filling is enhanced by verapamil, both at rest and during exercise. These mechanisms may account in part for the symptomatic improvement in many patients during verapamil therapy.

VERAPAMIL is an effective antianginal agent in many patients with coronary artery disease,1-3 and it is likely that, in some of these patients, symptomatic benefit may be ascribed to relief of underlying coronary spasm.4-6 However, the drug improves symptoms and exercise capacity in patients without overt evidence of spasm;4 the mechanisms by which verapamil exerts its salutary effects in such patients are most likely interrelated.

In addition to its beneficial symptomatic effects, verapamil also has the capacity, at least under experimental conditions, to reduce myocardial contractile function.7-8 While previous studies in patients with coronary artery disease9 have shown that left ventricular ejection fraction, mean velocity of circumferential fiber shortening, and stroke volume increase after i.v. verapamil (presumably as a result of reductions in systemic arterial pressure and vascular resistance9-10), the findings of these acute studies may not be applicable to the chronic situation, in which high doses of oral verapamil may lead to different effects at rest and particularly during exercise-induced myocardial ischemia.

Verapamil may also directly influence left ventricular relaxation and filling. It improves diastolic function in patients with hypertrophic cardiomyopathy,11,12 which may contribute to the enhanced exercise capacity experienced by many such patients during verapamil therapy.13 The majority of patients with coronary artery disease have abnormalities of diastolic filling, even in the absence of overt evidence of myocardial ischemia.14 Whether verapamil alters left ventricular relaxation and diastolic filling in patients with coronary artery disease, however, has not been investigated.

The purpose of the present investigation was to explore the basic physiologic effects of chronically administered oral verapamil on global left ventricular systolic function and diastolic filling, at rest and during exercise, in patients with coronary artery disease. To appreciate more fully the spectrum of actions of this calcium-channel inhibitor, the effects of oral propranolol were compared with those of verapamil in a subgroup of patients.

Methods

Patient Selection

We evaluated 16 patients, ages 29–64 years (mean 54 years), admitted to the National Heart, Lung, and Blood Institute for evaluation of coronary artery disease. The patients, 14 men and two women, all complained of angina pectoris despite therapy with propranolol and long-acting nitrate preparations. Seven patients had documented previous myocardial infarction and seven had previously undergone coronary artery bypass surgery (one of whom had undergone two coronary bypass operations). Seven patients had neither suffered a myocardial infarction nor un-
derned coronary bypass surgery. Only one patient had previous clinical evidence of left ventricular failure. Ten patients were in New York Heart Association functional class III and six patients were in functional class IV.

Left-heart catheterization and coronary arteriography were performed in 10 patients during hospitalization. In the other six, coronary arteriograms obtained between 1 month and 2 years before admission were reviewed. All patients had ≥75% reduction in luminal diameter of at least one major coronary artery: Two patients had ≥75% stenosis of one coronary artery, three had two-vessel disease (≥75% stenosis of one coronary artery and 50–100% stenosis of a second artery), and 11 had three-vessel disease (≥75% stenosis of two major coronary arteries and 50–100% stenosis of the remaining artery). The seven patients with previous coronary artery bypass operations all underwent repeat coronary arteriography 6 months after operation to assess graft patency. In these seven patients, only seven of 15 grafts were patent. No patient had all diseased vessels supplied by patent grafts.

**Drug Administration**

Twelve of the 16 patients constituted the basis of a previous report on the effects of verapamil on exercise tolerance in patients with chronic stable angina pectoris. To determine the “best dose” of β-adrenergic blocking agents in each patient, these patients and their private physicians were contacted 1 month before admission and instructed to increase the dosage of propranolol until angina pectoris was abolished or until distressing side effects (dyspnea, fatigue, depression, memory loss and impotence) were noted. Despite achieving heart rates of less than 60 beats/min, all 12 patients continued to complain of angina during best-dose propranolol therapy, which ranged from 160–320 mg/day (median 240 mg/day). After admission, propranolol was tapered and discontinued. At least 48 hours after cessation of propranolol, each patient entered a randomized crossover drug protocol including best-dose propranolol, placebo and verapamil. Each drug was administered in equally divided doses every 6 hours. Radionuclide studies were performed 48 hours after the initiation of propranolol and placebo. The initial verapamil dosage was 320 mg/day; after 48 hours, the dosage was increased to 480 mg/day. Radionuclide studies were performed after 48 hours of the higher dose of verapamil. The radionuclide tests were performed at the same time of day in each patient. Blood pressure and heart rate were measured in the supine position at the time of each radionuclide test. After each drug phase of the study, there was a 24-hour down-titration period (dosages halved for two doses and then quartered for two doses), followed by 24 hours free from all medications before treatment with the next drug. The time for completion of all three radionuclide studies ranged from 9–29 days (mean 13 days).

In the Results section, data obtained during treatment with placebo are included as control data. Eleven of these 12 patients, after completing the triple-crossover, randomized drug study, were also studied during combined treatment with best-dose propranolol and verapamil (480 mg daily). One of the 12 patients had transient asymptomatic atrioventricular dissociation while receiving high-dose verapamil, and therefore did not receive combined propranolol and verapamil.

In the four patients who did not take part in the randomized drug study, radionuclide studies were performed during control conditions and during verapamil therapy. The control study was performed at least 48 hours after the cessation of propranolol in each patient. After the control study, oral verapamil was initiated at a dose of 320 mg/day in divided doses. After 48 hours, the dose was increased to 480 mg/day. The radionuclide studies were repeated after 48 hours of the higher dose of verapamil. The interval between the control and verapamil study was 4–6 days in each patient. Blood pressure and heart rate were measured in the supine position at the time of each radionuclide study.

Several patients required nitroglycerin and long-acting nitrate preparations during the control and drug phases of the study. However, no patient received nitrate preparations within 6 hours of the radionuclide cineangiograms.

**Radionuclide Cineangiography**

Gated equilibrium blood pool cardiac scintigraphy was performed with the patient in the supine position. Before imaging, red blood cells were labeled in vivo with 15–20 mCi of technetium-99m. Imaging was accomplished using a conventional Anger camera equipped with a high-sensitivity, parallel-hole collimator oriented in a modified left anterior oblique position to isolate the left ventricle. A computer-based procedure gated to the ECG, previously described, was used to collect and organize data into a series of images or frames (framing rate up to 100 frames/sec) spanning the average cardiac cycle, which were displayed in a rapid-sequence, endless-loop format. After left ventricular and background regions of interest were labeled, high-temporal-resolution (10–20 msec/frame) time-activity curves were generated by summing the radioactivity in the ventricle during many beats. Cardiac cycles that fell outside a physician-selected range of acceptable cardiac cycle lengths were automatically excluded from analysis to prevent distortion of the time-activity curve by extrasystoles, postextrasystolic cycles, and wide variations in sinus cycle length. Exclusion of cardiac cycles of extremely long or short cycle length preserves the portion of the time-activity curve describing left ventricular diastolic events. Because blood radioactivity is proportional to blood volume, after background correction, the time-activity curve represents a measurement of relative left ventricular volume changes with time.

After images and time-activity curves were obtained at rest, imaging was repeated in each patient during supine bicycle exercise, except for one patient who could not exercise to a reproducible end.
point because of severe arthritis. Exercise studies were performed using a bicycle ergometer with a restraining harness to minimize patient motion under the camera. Exercise loads were increased in a stepwise fashion by 25 W at 2-minute intervals until the development of angina or limiting fatigue or dyspnea. In patients who developed angina, exercise continued until angina reached at least the severity typically causing the patient to stop exercising. Heart rate and blood pressure (by cuff sphygmomanometry) were monitored during exercise. For both control and drug studies, imaging was begun shortly after the onset of exercise, but only that portion of the data series that occurred during maximal symptom-limited exercise, encompassing the final 1.5–2 minutes of exercise, was selected for analysis.

Left ventricular ejection fraction at rest and during exercise was determined by computer analysis of the time-activity curves. Regional left ventricular function at rest and during exercise was determined subjectively by two observers by visual inspection of the radionuclide movies and by inspection of the count-based functional stroke volume map (or "difference image"), constructed by computer subtraction of the end-diastolic image from the end-systolic image. Peak left ventricular ejection rate and filling rate, at rest and during exercise, were then computed as previously described, by fitting a third-order polynomial function to the systolic ejection and rapid diastolic filling portions of the time-activity curves using a least-squares technique. The time to peak filling rate (measured from end-systole to the time of peak left ventricular filling rate) was then determined. Both peak ejection rate and peak filling rate were computed in left ventricular counts per second; these values were normalized for the number of left ventricular counts at end-diastole and expressed as end-diastolic counts per second (EDV/sec). This does not assume knowledge of actual left ventricular end-diastolic volume.

Several variables were used to describe global left ventricular systolic function. These were left ventricular ejection fraction, peak left ventricular ejection rate, and left ventricular ejection time (measured from the R wave to end-systole). The peak left ventricular filling rate and time to peak filling rate were used to express left ventricular diastolic filling. The validity of determining these variables from gated time-activity curves has been described.

Normal values of the variables describing resting left ventricular systolic function and diastolic filling, determined in 45 normal volunteers, have been reported in detail and are presented in table 1, along with the values obtained during maximal supine exercise. The normal volunteers, ages 21–63 years, had no cardiac symptoms and had normal physical examinations, chest x-rays, ECGs and echocardiograms. During radionuclide testing, no volunteer developed chest pain.

### Statistical Methods

Data were analyzed by the t test, using paired and unpaired data, and by linear regression analysis as appropriate.

### Results

#### Control Measurements

#### Rest

*Left ventricular systolic function.* Left ventricular ejection fraction at rest ranged from 32–69% (mean 50 ± 10% [±SD], table 2). Ejection fraction was subnormal at rest (less than 45%) in three of the 16 patients. Values of peak ejection rate and ejection time are listed in table 2.

*Left ventricular diastolic filling.* Peak left ventricular filling rate at rest (table 2) ranged from 1.2–3.1 EDV/sec (mean 1.9 ± 0.6 EDV/sec). Peak filling rate was subnormal (less than 2.5 EDV/sec) in 14 of the 16 patients, including 11 of the 13 patients with normal left ventricular ejection fraction (fig. 1). Peak filling rate at rest correlated with ejection fraction at rest (r = 0.84, r² = 0.71). Time to peak filling rate (table 2) ranged from 125–269 msec at rest (mean 185 ± 38 msec) and exceeded the upper limit of normal, 180 msec, in 11 patients. Since peak filling rate did not correlate with time to peak filling rate (r = 0.004), both variables were used as independent measures of left ventricular diastolic filling. When combined analysis of the two diastolic filling variables was

| TABLE 1. Variables Describing Left Ventricular Systolic Function and Diastolic Filling in 45 Normal Volunteers |
|-------------------------------------------------|-----------------|-----------------|
| Rest*                                           | Maximal supine  |
|                                                 | bicycle exercise|
|                                                 | Range          | Mean ± SD       | Range          | Mean ± SD |
| Heart rate (beats/min)                          | 56–110         | 75 ± 14         | 115–184        | 145 ± 19  |
| LV systolic function                            |                |                 |                |
| Ejection fraction (%)                           | 45–72          | 55 ± 6          | 56–90          | 68 ± 7    |
| Peak ejection rate (EDV/sec)                    | 1.9–3.7        | 2.7 ± 0.5       | 2.7–7.1        | 4.2 ± 1.2 |
| Ejection time (msec)                            | 260–450        | 344 ± 33        | 180–290        | 237 ± 29  |
| LV diastolic filling                            |                |                 |                |
| Peak filling rate (EDV/sec)                     | 2.5–5.0        | 3.3 ± 0.6       | 3.6–8.5        | 6.2 ± 1.3 |
| Time to peak filling rate (msec)                | 90–180         | 136 ± 23        | 58–130         | 88 ± 17   |

*The data at rest have been reported in detail. Abbreviations: EDV = end-diastolic volume; LV = left ventricular.*
performed, in 15 patients the values fell outside the normal range. The only patient whose diastolic filling variables were normal had borderline values for both peak filling rate (2.6 EDV/sec) and time to peak filling rate (180 msec). Neither peak filling rate nor time to peak filling rate correlated with heart rate under resting conditions* (r = 0.003 and r = 0.34, respectively).

**Exercise**

Left ventricular systolic function. In the 15 patients studied during maximal supine exercise, exercise was terminated in every patient because of angina. Left ventricular ejection fraction during exercise ranged from 23–64% (mean 42 ± 13%) (table 2). This represents a decrease in ejection fraction compared with the resting value in 12 patients, and an increase compared with the resting value in the other three (fig. 2). Of the three patients whose ejection fraction increased during exercise, one patient had 100% occlusion of the right coronary artery, with left-to-right collaterals filling a diffusely diseased distal vessel, one patient had > 75% stenosis of all three major coronary arteries, and one patient had 100% stenosis of both the left anterior descending and circumflex arteries and > 75% stenosis of the right coronary artery. Two of these three patients manifested regional wall motion abnormalities during exercise that were not present at rest. For the group as a whole, ejection fraction during exercise was lower than that measured at rest (p < 0.05). The peak ejection rate and ejection time are listed in table 2.

**FIGURE 1.** Peak left ventricular (LV) filling rate at rest plotted as a function of LV ejection fraction at rest. The dashed lines indicate the lower limits of normal for peak filling rate (2.5 EDV/sec) and ejection fraction (45%). The stippled region indicates the expected normal range.
Left ventricular diastolic filling. Peak left ventricular filling rates were significantly greater during exercise (table 2) compared with the resting values (3.1 ± 0.9 during exercise, 1.9 ± 0.6 EDV/sec at rest, p < 0.001). Similarly, time to peak filling rate decreased during exercise (108 ± 30 during exercise, 185 ± 38 msec at rest, p < 0.001). Although these changes represent an increase in the rate of diastolic filling during maximal exercise, the values are still diminished compared to exercise data from normal volunteers. Peak filling rate during maximal exercise in the normal subjects ranged from 3.7–8.5 EDV/sec (mean 6.1 ± 1.0 EDV/sec) (table 1).

Effect of Verapamil

Rest

Resting heart rate decreased during verapamil therapy (table 2, fig. 3) from a control value of 76 ± 12 to 69 ± 11 beats/min (p < 0.005). Verapamil also resulted in significant reductions in systolic and diastolic blood pressure (table 2).

Left ventricular systolic function. Left ventricular ejection fraction at rest diminished during verapamil therapy (table 2, fig. 3), from 50 ± 10% before to 45 ± 12% during verapamil (p < 0.005), a change that did not correlate with either the change in heart rate (r = 0.41) or in systemic blood pressure during verapamil (r = 0.16 for systolic and r = 0.38 for diastolic pressure). Ejection fraction decreased during verapamil in all but three patients. Peak left ventricular ejection rate and left ventricular ejection time were not altered by verapamil (table 2).

Left ventricular diastolic filling. Peak left ventricular filling rate at rest increased (table 2, fig. 3) from 1.9 ± 0.6 EDV/sec before to 2.3 ± 0.9 EDV/sec during verapamil (p < 0.005), with only two patients manifesting a decrease. Time to peak filling rate decreased during verapamil (from 185 ± 38 msec to 161 ± 27 msec, p < 0.05), with only four patients manifesting an increase (fig. 3). Concordant evidence of improved left ventricular diastolic filling during verapamil (both an increase in peak filling rate and a reduction in time to peak filling rate) was observed in 11 of 16 patients (69%). An example of improved diastolic filling during verapamil is shown in figure 4.

The change in peak filling rate at rest during verapamil (fig. 5) correlated with the change in left ventricular ejection fraction at rest (r = 0.74, r² = 0.55), such that patients with the greatest decrease in ejection fraction during verapamil demonstrated the least improvement in peak filling rate. The two patients whose peak filling rate decreased during verapamil were the two patients with the greatest reduction in ejection fraction. Changes in time to peak filling rate during verapamil did not correlate (r = 0.28) with changes in ejection fraction (fig. 5). However, three of the four patients whose time to peak filling rate did not shorten during verapamil had the greatest reduction in ejection fraction during verapamil. Neither the changes in peak filling rate nor the changes in time to peak filling rate during verapamil correlated with changes in heart rate of systemic blood pressure.

Exercise

Maximal heart rate during exercise was reduced by verapamil (110 ± 9 beats/min control vs 104 ± 7 verapamil, p < 0.05) (table 2, fig. 6). Systolic and diastolic blood pressure at maximal exercise was also lower during verapamil compared with control. During verapamil therapy, 11 of 15 patients terminated exercise because of angina. Eight patients achieved higher exercise work loads during verapamil than during control conditions (one additional 25-W stage in seven patients and two stages in one patient), six achieved the same work load, and one terminated exercise at a lower work load (125 W control vs 75 W during verapamil).

Left ventricular systolic function. Left ventricular ejection fraction during exercise was not altered by verapamil (42 ± 13% control, 43 ± 12% verapamil) (table 2, fig. 6). Hence, since verapamil reduced rest-
ing ejection fraction but did not change exercise ejection fraction, the magnitude of the reduction in ejection fraction that occurred from rest to exercise under control conditions appeared improved (table 3, fig. 7). The decrease in ejection fraction from rest to exercise diminished from -7 ± 11% under control conditions to -2 ± 11% with verapamil (p < 0.01). Neither the change in exercise ejection fraction (fig. 6) nor the change in the ejection fraction response to exercise (fig. 7) was related to the change in work load achieved during verapamil. Peak left ventricular ejection rate and left ventricular ejection time during exercise were not changed during verapamil therapy compared with control values (table 2).

Left ventricular diastolic filling. Peak left ventricular filling rate during maximal exercise increased with verapamil therapy (3.1 ± 0.9 EDV/sec control, 3.6 ± 1.1 EDV/sec verapamil; p < 0.05) (table 2, fig. 6). Peak filling rate during exercise decreased in only two patients with verapamil. (These are not the same patients whose peak filling rate at rest was decreased by verapamil.) Time to peak filling rate during exercise decreased during verapamil (108 ± 30 msec control, 91 ± 17 verapamil; p < 0.05). Verapamil increased this variable in only three patients (fig. 6). Unlike the changes in peak filling rate induced by verapamil at rest, the changes during maximal exercise did not correlate with the changes in exercise ejection fraction (r = 0.16). Changes in exercise peak filling rate and time to peak filling rate also did not correlate with the changes in exercise heart rate and exercise blood pressure. Moreover, the changes in the diastolic filling variables during exercise did not correlate with the change in the exercise load achieved during verapamil (fig. 6); the changes in the diastolic filling variables in the 11 patients who developed angina during exercise while receiving verapamil also did not differ from the four who did not experience angina.

Effects of Verapamil vs Propranolol

Rest

In the subgroup of patients who were also studied during propranolol therapy, heart rate at rest was lower than control values during both propranolol and verapamil (table 4). Heart rate during propranolol (56 ± 8 beats/min) was significantly lower than that observed during verapamil (71 ± 10 beats/min, p <
Figure 5. The change in peak left ventricular (LV) filling rate at rest (top) and the change in time to peak LV filling rate at rest (bottom) plotted as functions of the change in resting LV ejection fraction (EF) during verapamil. Improvements in peak filling rate are indicated by positive changes (stippled area), and improvements in time to peak filling rate by negative changes (stippled area).

0.001). Effects of the two drugs on systemic blood pressure were not different.

Left ventricular systolic function. Although verapamil decreased left ventricular ejection fraction at rest to a greater extent from control than did propranolol (table 4), the levels of ejection fraction attained on each of the two drugs were not significantly different (46 ± 8% propranolol, 44 ± 12% verapamil). There was also no difference between the effects on peak left ventricular ejection rate. In this subgroup of patients, verapamil prolonged left ventricular ejection time compared to control (p < 0.05); during propranolol, ejection time was more prolonged (372 ± 22 msec propranolol, 343 ± 29 msec verapamil; p < 0.05).

Left ventricular diastolic filling. In this subgroup of patients, the effects of verapamil on the diastolic filling variables at rest were similar to those observed in the larger group of 16 patients. Thus, peak left ventricular filling rate increased during verapamil (p < 0.01) and time to peak filling rate decreased (p < 0.05). Propranolol did not change either variable (table 4). Although peak filling rate was higher during verapamil (2.3 ± 0.9 EDV/sec) compared with propranolol (1.9 ± 0.7 EDV/sec, p < 0.05), time to peak filling rate was not significantly different (169 ± 27 msec propranolol, 161 ± 26 msec verapamil). Relative effects of propranolol and verapamil on the left ventricular volume curves are shown in figure 8.

Exercise

During exercise in this subgroup of patients, propranolol lowered maximum heart rate to a greater degree than did verapamil (to 87 beats/min with
propranolol vs 106 ± 5 beats/min with verapamil, *p* < 0.001). The two drugs exerted similar effects on blood pressure (table 4). Six of 12 patients terminated exercise because of angina both during propranolol and during verapamil; three other patients developed angina during propranolol but not verapamil, and the three remaining patients developed angina during verapamil but not propranolol. Six patients achieved the same exercise work load during both propranolol and verapamil, three patients achieved higher work loads during propranolol, and three patients achieved higher work loads during verapamil.

**Left ventricular systolic function.** Neither verapamil nor propranolol altered left ventricular ejection fraction during exercise (table 4). Since propranolol did not significantly reduce ejection fraction at rest or during exercise, propranolol did not significantly change the magnitude of the difference in ejection fraction.

Left ventricular systolic function. Neither verapamil nor propranolol altered left ventricular ejection fraction during exercise (table 4). Since propranolol did not significantly reduce ejection fraction at rest or during exercise, propranolol did not significantly change the magnitude of the difference in ejection fraction.

---

**Figure 7.** The magnitude of the change in left ventricular (LV) ejection fraction from rest to exercise under control conditions and during verapamil. Symbols are explained in figure 6.

**Figure 8.** Time-activity curves obtained at rest from a patient during control conditions, during propranolol, and during verapamil. Ejection fraction was not altered by either drug. Propranolol did not alter early rapid diastolic filling, but prolonged the diastasis period by increasing the cycle length. In contrast, verapamil did not change heart rate compared with control (69 beats/min), but increased the peak filling rate and decreased the time to peak filling rate.
fraction between rest and exercise (table 3). Verapamil did not alter peak ejection rate or ejection time compared to control. Propranolol decreased peak ejection rate ($p < 0.01$) and prolonged ejection time ($p < 0.001$) during exercise compared to verapamil values.

In the three patients who did not develop angina with exercise during propranolol, the exercise ejection fraction was higher during propranolol than during control in all three (39 ± 9% vs 36 ± 10%). A similar observation was made in the three patients who did not develop angina during verapamil, who all had higher exercise ejection fractions during verapamil (49 ± 13% verapamil, 43 ± 10% propranolol).

**Left ventricular diastolic filling** Verapamil increased peak filling rate during exercise ($p < 0.005$) and decreased time to peak filling rate ($p < 0.05$) compared with control values (table 4). Propranolol did not alter either variable. Hence, peak filling rate during verapamil was higher than that during propranolol ($p < 0.001$) and time to peak filling rate was shorter ($p < 0.005$). These different effects of propranolol and verapamil on left ventricular filling did not correlate with either the exercise work load achieved during each drug or the development of angina during exercise.

**Combined Verapamil and Propranolol Administration**

**Rest**

In the 11 patients studied during combined administration of verapamil and propranolol, heart rate during both drugs (57 ± 8 beats/min) was no different than during propranolol alone, but was significantly lower than control and verapamil alone (table 5). Combined drug administration did not alter any of the resting systolic function or diastolic filling vari-

---

**Table 4. Effect of Propranolol and of Verapamil in 12 Patients with Coronary Artery Disease**

<table>
<thead>
<tr>
<th></th>
<th>Control (mean ± sd)</th>
<th>Propranolol (mean ± sd)</th>
<th>Verapamil (mean ± sd)</th>
<th>$p$ propranolol vs verapamil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rest</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>77 ± 13</td>
<td>56 ± 8§</td>
<td>71 ± 10†</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>139 ± 23</td>
<td>132 ± 20</td>
<td>124 ± 20†</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic</td>
<td>82 ± 12</td>
<td>74 ± 7*</td>
<td>74 ± 12†</td>
<td>NS</td>
</tr>
<tr>
<td>LV systolic function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>48 ± 9</td>
<td>46 ± 8</td>
<td>44 ± 12*</td>
<td>NS</td>
</tr>
<tr>
<td>Peak ejection rate (EDV/sec)</td>
<td>2.4 ± 0.4</td>
<td>2.0 ± 0.3†</td>
<td>2.2 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection time (msec)</td>
<td>326 ± 43</td>
<td>372 ± 22‡</td>
<td>343 ± 29*</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>LV diastolic filling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak filling rate (EDV/sec)</td>
<td>1.9 ± 0.6</td>
<td>1.9 ± 0.7</td>
<td>2.3 ± 0.9†</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Time to peak filling rate (msec)</td>
<td>185 ± 42</td>
<td>169 ± 27</td>
<td>161 ± 26*</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Maximal exercise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>112 ± 9</td>
<td>87 ± 4§</td>
<td>106 ± 5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>167 ± 21</td>
<td>157 ± 16</td>
<td>147 ± 10*</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic</td>
<td>91 ± 8</td>
<td>87 ± 5</td>
<td>86 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>LV systolic function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>41 ± 11</td>
<td>41 ± 8</td>
<td>42 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Peak ejection rate (EDV/sec)</td>
<td>2.1 ± 0.7</td>
<td>1.7 ± 0.4</td>
<td>2.1 ± 0.6</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Ejection time (msec)</td>
<td>305 ± 31</td>
<td>348 ± 21§</td>
<td>294 ± 17</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LV diastolic filling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak filling rate (EDV/sec)</td>
<td>3.1 ± 0.9</td>
<td>2.7 ± 0.6</td>
<td>3.5 ± 1.0†</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time to peak filling rate (msec)</td>
<td>102 ± 27</td>
<td>114 ± 21</td>
<td>88 ± 21*</td>
<td>&lt; 0.005</td>
</tr>
</tbody>
</table>

Statistical significance compared with control data:

* $p < 0.05$.
† $p < 0.01$.
‡ $p < 0.005$.
§ $p < 0.001$.

Abbreviations: See table 2.
ables compared with values during administration of propranolol alone. Although combined treatment reduced left ventricular ejection fraction compared with control (table 5), it did not significantly reduce ejection fraction below that attained by verapamil alone. Two patients, however, did show a 5% or greater reduction in ejection fraction during combined therapy compared with that during verapamil therapy. Combined drug administration did reduce peak ejection rate compared with values during verapamil alone. Combined drug treatment did not consistently change the diastolic filling variables beyond the improvement induced by verapamil alone (table 5).

Exercise
Heart rate at maximal exercise during combined drug administration (79 ± 7 beats/min) was significantly lower than that achieved under control conditions, during verapamil alone and during propranolol alone (table 5). Only four of 11 patients terminated exercise because of angina during combined drug therapy. The effects of combined drug treatment on left ventricular ejection fraction during exercise did not differ from those during control. Hence, as a result of the reduction in resting ejection fraction, combined drug treatment, like verapamil, reduced the magnitude of the reduction that occurred in ejection fraction from rest to exercise (table 3). Combined drug treatment did not alter exercise peak filling rate compared with control and propranolol values, but significantly reduced exercise peak filling rate compared with verapamil values (p < 0.005, table 5). Because of the large standard deviation in this subgroup of patients, time to peak filling rate was no different during combined treatment compared to control, verapamil alone and propranolol alone.

Regional Left Ventricular Function
Under control conditions, regional wall motion abnormalities were observed at rest in nine patients, including six of the 13 patients with normal resting left ventricular ejection fraction. During exercise, regional wall motion abnormalities were observed in all but one patient, who had the highest value of ejection fraction during exercise. By qualitative analysis of regional wall motion, neither verapamil administration, propranolol administration, nor combined therapy appreciably altered these regional wall motion abnormalities at rest or during exercise.

Discussion
Oral verapamil therapy improves exercise tolerance and reduces the frequency of angina pectoris in many patients with coronary artery disease.1-4 Hence, verapamil appears to be an effective therapeutic alternative to β-adrenergic blocking drugs; it is especially useful in patients refractory to or experiencing important side effects from β-blocking drugs.4

Verapamil consistently reduces heart rate and blood pressure in patients with coronary artery disease under resting conditions, and usually decreases heart rate, blood pressure and the rate-pressure product during exercise.5-4 In contrast, propranolol results in a more pronounced decrease in exercise heart rate than verapamil;4 since propranolol also reduces exercise blood pressure, the rate-pressure product is consistently diminished.4,21-24 Hence, while the antianginal effects of verapamil can be attributed, at least in part, to its capacity to reduce heart rate and blood pressure, two important determinants of myocardial oxygen consumption, the improvement in the rate-pressure product is often very small and considerably less than that after propranolol.4 Thus, additional mechanisms may play a role in the antianginal properties of verapamil.

Such mechanisms may derive, at least in part, from the depressive action this calcium-channel blocking agent may exert on left ventricular contractile function.5,6 On the basis of the effects of verapamil on left ventricular diastolic function in patients with hypertrophic cardiomyopathy,7,11,12 we also hypothesized that the calcium-inhibitory effects of verapamil may alter left ventricular relaxation and, thereby, left ventricular filling in patients with coronary artery disease. If such changes in contractile function and relaxation occurred, they could affect either myocardial oxygen requirements, myocardial oxygen delivery or both. Therefore, to determine if verapamil alters left ventricular systolic or diastolic function in a clinical setting, we performed radionuclide cineangiography at rest and during exercise to assess the influence of oral verapamil on left ventricular contractile function and diastolic filling in patients with coronary artery disease, and compared the effects of verapamil with those of propranolol. The dose of verapamil we administered, 480 mg/day, was chosen because it has been found to improve exercise capacity and relieve angina to a greater extent than a dose of 320 mg/day.4

Left Ventricular Systolic Function
Verapamil significantly reduced resting left ventricular ejection fraction (table 2, fig. 3), although systemic blood pressure also decreased, a change that would have been expected to facilitate an increase in ejection fraction. These data suggest that at the relatively high doses necessary to provide a maximal antianginal effect, the direct negative inotropic effects of verapamil may override the beneficial influences its peripheral and coronary vasodilatory actions may exert on left ventricular contractile function.

A reduction in left ventricular contractile function produced by verapamil may diminish myocardial oxygen requirements and thereby contribute to the drug's antianginal effect. However, the fact that verapamil does not decrease left ventricular contractile function during exercise minimizes the likelihood that this action contributes to the drug's salutary influences in angina pectoris. Moreover, verapamil-induced depression of resting ejection fraction may, in some patients, be deleterious. For example, the patient with the greatest reduction in ejection fraction after verapamil developed overt pulmonary edema while on chronic verapamil therapy after discharge from hospital. Two other study patients complained of dyspnea
VERAPAMIL EFFECTS ON LV FUNCTION IN CAD/Bonow et al.

**Table 5. Effect of Combined Verapamil and Propranolol in 11 Patients with Coronary Artery Disease**

<table>
<thead>
<tr>
<th></th>
<th>Verapamil and propranolol (Mean ± sd)</th>
<th>Statistical difference (p) compared with</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Verapamil</td>
</tr>
<tr>
<td>Rest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>55 ± 5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>117 ± 15</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Diastolic</td>
<td>72 ± 7</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>LV systolic function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>43 ± 10</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Peak ejection rate (EDV/sec)</td>
<td>1.8 ± 0.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ejection time (msec)</td>
<td>396 ± 41</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LV diastolic filling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak filling rate (EDV/sec)</td>
<td>2.2 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Time to peak filling rate (msec)</td>
<td>148 ± 241</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Maximal exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>79 ± 7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>142 ± 18</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Diastolic</td>
<td>84 ± 4</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>LV systolic function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>41 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Peak ejection rate (EDV/sec)</td>
<td>1.7 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection time (msec)</td>
<td>355 ± 25</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LV diastolic filling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak filling rate (EDV/sec)</td>
<td>2.9 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Time to peak filling rate (msec)</td>
<td>115 ± 36</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: See table 2.

during the hospitalization while on combined verapamil and propranolol therapy; this responded to a reduction in verapamil dose. We have also documented pulmonary edema in two patients with coronary artery disease (not included in the current study) during oral verapamil, 480 mg/day, that was reversed after verapamil therapy was terminated. Those patients had normal resting ejection fractions before verapamil. Of note, the patients in whom verapamil exerted the greatest reduction in ejection fraction also developed worsening of left ventricular diastolic filling at rest, manifested by a reduction in peak filling rate and a prolongation of time to peak filling rate (fig. 5). Whether the deterioration of systolic or of diastolic function in these patients contributes more importantly to clinical deterioration is unclear.

Borer et al. suggested that the magnitude of the reduction in ejection fraction that usually occurs from rest to exercise in patients with coronary artery disease might provide a measure of the extent of reversible myocardial ischemia. Verapamil diminished this reduction in ejection fraction (table 3, fig. 7), a change that could be interpreted as beneficial. However, it was caused by a verapamil-induced decrease in resting ejection fraction rather than by an increase in exercise ejection fraction. Hence, the physiologic significance of this improvement is questionable.

The effects of oral propranolol differed from those of verapamil. The different effects of propranolol and verapamil on resting ejection fraction might be related to differences in heart rates during the two drugs or possibly between different effects on left ventricular end-diastolic volume (which we did not measure with our noninvasive technique). Although propranolol did not alter left ventricular ejection fraction at rest (table 4), it did significantly reduce peak ejection rate. Similar findings were noted during exercise. Although the results regarding the lack of effect of propranolol on resting ejection fraction are similar to those of previous investigations, some investigators have reported that propranolol does not alter resting ejection rate and improves exercise ejection fraction. These disparate results may be in part ex-
plained by methodologic differences (such as upright exercise\textsuperscript{25, 26} and linear curve-fitting\textsuperscript{25, 26} to compute ejection rate compared with our technique), and possibly by patient selection. Our patients were all selected on the basis of anginal symptoms refractory to propranolol, and nine of 12 patients developed angina during exercise while receiving propranolol. However, in the three patients who were angina-free during propranolol, propranolol resulted in consistently higher exercise ejection fractions. Apparently, when propranolol can prevent exercise-induced ischemia, deterioration of left ventricular function during exercise can be prevented.\textsuperscript{24}

The combination of verapamil and propranolol did not decrease ejection fraction at rest below the reduced level produced by verapamil alone; as with verapamil alone and propranolol alone, the combination did not alter ejection fraction during exercise. In our previous study, combined administration of verapamil and propranolol was more effective in improving exercise tolerance than either drug alone.\textsuperscript{4} This improved functional result is therefore not achieved at the expense of a further deterioration in left ventricular contractile function.

**Left Ventricular Diastolic Filling**

Impaired left ventricular diastolic filling at rest, assessed noninvasively by radionuclide cineangiography, often occurs in patients with coronary artery disease, even when resting regional and global left ventricular systolic function is normal and there is no evidence of previous myocardial infarction.\textsuperscript{14} Fifteen of the 16 patients in the current study demonstrated abnormalities of diastolic filling at rest, manifested by diminished peak left ventricular filling rate, prolonged time to peak filling rate, or both, although left ventricular ejection fraction at rest was normal in 13 of these patients (fig. 1). Although peak filling rate increased and time to peak filling rate decreased in every patient during exercise (table 2), the values were still abnormal compared with exercise data of normal volunteers (table 1). However, because normal persons have a characteristically different ejection fraction response to exercise than do patients with coronary artery disease,\textsuperscript{17} because peak filling rate is directly related to ejection fraction\textsuperscript{44} (fig. 1), and because changes in ejection fraction are associated with changes in peak filling rate (fig. 5), the meaning of the differences in diastolic variables during exercise between normal subjects and patients with coronary artery disease is questionable. That diastolic filling is impaired during exercise-induced angina, however, is supported by previous observations of abnormal isovolumic relaxation and diastolic distensibility during angina induced by exercise or by rapid atrial pacing.\textsuperscript{41-43} While impaired left ventricular diastolic function may be a reflection of myocardial ischemia in patients with coronary artery disease, diastolic dysfunction may also contribute to the development of ischemia. Impairment of isovolumic relaxation with reduction in the rate of decrease of early diastolic ventricular wall tension may impede regional antegrade and collateral coronary flow. Alterations in left ventricular compliance, with increased left ventricular diastolic pressures, may aggravate end-diastolic wall stress and increase myocardial oxygen requirements.

During verapamil administration, diastolic filling variables improved significantly at rest (table 2, fig. 3). This improvement is similar to that previously reported in patients with hypertrophic cardiomyopathy.\textsuperscript{11, 12} However, these results contradict those of Rousseau et al.,\textsuperscript{48} who reported no improvement in left ventricular relaxation at rest (assessed by peak negative dP/dt and the time constant [T]) in patients with coronary artery disease after intracoronary nifedipine, another calcium-channel blocking agent. These disparate results may reflect either differences in methods (Rousseau et al. assessed left ventricular pressure changes during acute intracoronary therapy, whereas we assessed left ventricular volume changes during chronic oral therapy) or differences between the effects of verapamil and nifedipine on the diastolic properties of the left ventricle. Our results also demonstrate that verapamil improves left ventricular diastolic filling during exercise (table 2, fig. 6). This improvement in left ventricular filling during exercise did not depend upon whether patients could achieve higher work loads while receiving verapamil (fig. 6).

Several mechanisms may explain the improvement in left ventricular diastolic filling during verapamil. Experimental evidence suggests that disturbances of intracellular calcium metabolism during myocardial ischemia\textsuperscript{39} may account, at least in part, for the findings of incomplete or impaired relaxation,\textsuperscript{26-32, 38, 37} altered diastolic tone,\textsuperscript{29, 30} and tension prolongation during recovery from hypoxia.\textsuperscript{39, 40} Impaired myocardial relaxation during hypoxia appears to be reversible under some experimental conditions and may be modified by intracellular calcium availability.\textsuperscript{41, 42} Impaired left ventricular relaxation and filling during and after ischemia may, therefore, be improved by verapamil and other agents that reduce calcium ion flux across the myocardial membrane.

Left ventricular relaxation and filling are dependent not only upon inactivation of the events causing contraction, but also upon the loading conditions of the left ventricle.\textsuperscript{43} Hence, factors in addition to those that alter intracellular calcium metabolism might account for the changes we observed in left ventricular filling during verapamil. For example, heart rate, left ventricular contractility and systemic blood pressure are important loading variables that may influence relaxation and filling of the left ventricle,\textsuperscript{46, 44} and all three variables were affected by verapamil. The directional changes caused by verapamil, however, would have been expected to lead to a decrease in the rate of ventricular filling, in that (1) a reduction in heart rate is associated with a decrease in peak filling rate and prolongation of time to peak filling rate,\textsuperscript{46} (2) lower left ventricular ejection fractions are associated with lower peak filling rates,\textsuperscript{14} and (3) reductions in systemic blood pressure decrease the rate of ventricular relaxation.\textsuperscript{45} Thus, the increase in peak filling rate and decrease in time to peak filling rate produced by
verapamil appeared to occur despite verapamil's effects on heart rate, left ventricular contractile state and systemic blood pressure. These effects of verapamil on heart rate, contractile state and blood pressure, by reducing myocardial oxygen requirements, may reduce myocardial ischemia, providing another mechanism by which left ventricular relaxation and filling are enhanced. We cannot discount possible improvement in myocardial diastolic filling. The actual mechanisms of improved diastolic filling induced by verapamil cannot be definitely determined using our noninvasive techniques.

In contrast to verapamil, propranolol affected neither peak filling rate nor time to peak filling rate at rest or during exercise (table 4, fig. 8). This lack of response may reflect our patient selection, since each patient's symptoms were refractory to propranolol. In addition, the lack of change in diastolic filling variables with propranolol is difficult to interpret because of greater decrease in heart rate, both at rest and during exercise, with propranolol than with verapamil (table 4). Preliminary studies using atrial pacing have demonstrated that a reduced heart rate is associated with a decreased peak filling rate and prolonged time to peak filling rate. Therefore, this tendency for propranolol to improve left ventricular filling might be counteracted by the reduced heart rate. The influence of heart rate on diastolic filling must also affect the diastolic filling data during combined therapy with verapamil and propranolol (table 5), since heart rates during exercise with combined therapy were significantly lower than those with either verapamil or propranolol alone. Hence, reversal of the favorable changes in diastolic filling induced by verapamil during exercise may have been due to the marked reduction in exercise heart rate during combined therapy.

In summary, the results of this study in patients with coronary artery disease demonstrate that left ventricular ejection fraction at rest is diminished when verapamil is administered orally at a dose of 480 mg/day, but that ejection fraction during exercise is unaltered. Despite the depression of resting left ventricular systolic function, verapamil improves left ventricular diastolic filling. The mechanisms of the antianginal effects of verapamil are most likely interrelated. The reduction in heart rate and blood pressure that often occurs both at rest and during exercise with verapamil should translate into reduced myocardial oxygen requirements. Moreover, the increase in peak left ventricular filling rate during verapamil, both at rest and with exercise, is probably a reflection of more rapid ventricular relaxation. If so, the more rapid relaxation would lead to a more rapid fall in early diastolic wall stress, which in turn would facilitate antegrade and collateral coronary flow. Further studies will be required to determine whether verapamil has selective effects on regional contractility, whether the improvements in global left ventricular diastolic filling are related to selective enhancement of regional myocardial relaxation, and whether improvements in diastolic filling are associated with improved left ventricular diastolic pressure-volume relations.

Acknowledgment

The authors appreciate the excellent technical assistance of Barbara Damske, Sharon Findley, and Susan Farkas in the acquisition of data and the preparation of this manuscript. We thank the Knoll Pharmaceutical Company, Whippany, New Jersey, for supplying us with verapamil (Isoptin).

References

5. Freedman B, Dunn RF, Richmond DR, Kelley DT: Coronary artery spasm: treatment with verapamil. (abstr) Circulation 60 (suppl II): II-249, 1979
16. Borer JS, Bacharach SL, Green MV, Kent KM, Epstein SE,


Effects of verapamil and propranolol on left ventricular systolic function and diastolic filling in patients with coronary artery disease: radionuclide angiographic studies at rest and during exercise.
R O Bonow, M B Leon, D R Rosing, K M Kent, L C Lipson, S L Bacharach, M V Green and S E Epstein

Circulation. 1982;65:1337-1350
doi: 10.1161/01.CIR.65.7.1337
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 American Heart Association, Inc. All rights reserved.
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:
http://circ.ahajournals.org/content/65/7/1337

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/