Verapamil-induced improvement in left ventricular diastolic filling and increased exercise tolerance in patients with hypertrophic cardiomyopathy: short- and long-term effects

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ABSTRACT  Verapamil improves exercise tolerance and decreases symptoms in many patients with hypertrophic cardiomyopathy. The mechanisms responsible for these effects are not completely understood, although previous studies indicate that verapamil enhances left ventricular relaxation and diastolic filling in such patients. To investigate the association between changes in left ventricular filling and exercise tolerance after verapamil, we studied 55 patients with hypertrophic cardiomyopathy by radionuclide angiography and graded treadmill testing before and after 1 to 4 weeks of therapy with orally administered verapamil, 320 to 640 mg/d. The verapamil-induced increase in peak left ventricular filling rate at rest (from 3.1 ± 1.3 to 3.7 ± 1.3 end-diastolic volumes/sec; p < .001) was associated with an increase in exercise tolerance (from 5.9 ± 3.6 to 8.7 ± 4.7 min; p < .001); exercise capacity increased in 34 of 43 patients (79%) manifesting an increase in peak filling rate but only one of 12 patients (8%) with unchanged or decreased peak filling rate (p < .001). This initial trend persisted in 25 patients studied after 1 year of therapy; 11 of 16 patients (69%) with a persistent increase in peak filling rate had persistent improvement in exercise tolerance relative to preverapamil values, compared with only one of nine patients (11%) in whom peak filling rate was unchanged or decreased relative to preverapamil levels (p < .02). Verapamil withdrawal after 1 to 2 years in 24 patients resulted in reduction in peak filling rate (p < .001) and was associated with deterioration in exercise tolerance in 17 patients (71%). Hence, verapamil-induced changes in left ventricular peak filling rate were associated significantly with objective symptomatic improvement. These data support the concept that enhanced left ventricular diastolic filling is an important mechanism contributing to the clinical improvement experienced by many patients with hypertrophic cardiomyopathy during therapy with verapamil.


IMPAIRED RELAXATION and diastolic filling of the left ventricle contribute importantly to the spectrum of symptoms experienced by patients with hypertrophic cardiomyopathy. Several studies of hypertrophic cardiomyopathy indicate that verapamil, administered intravenously or orally, improves indexes of left ventricular relaxation and diastolic filling.1-4 Verapamil also reduces symptoms and increases exercise tolerance in many patients with this disease.5-9 However, the relationship between enhanced left ventricular diastolic filling resulting from verapamil and improved exercise tolerance has not been demonstrated conclusively.

In this study, we investigated the association between improved left ventricular diastolic filling and improved exercise capacity induced by therapy with orally administered verapamil, both short- and long-term, in patients with hypertrophic cardiomyopathy. Left ventricular diastolic filling characteristics were assessed by radionuclide angiography, and exercise tolerance was measured objectively by graded treadmill exercise testing. To evaluate further the interrelationship between left ventricular diastolic filling and exercise capacity and the reversible effects of verapamil, we also studied the effects of verapamil withdrawal after long-term therapy in a subgroup of patients.

Methods

Patient selection. We studied the effects of verapamil administered orally in a total of 70 patients with hypertrophic...
cardiomyopathy by radionuclide angiography and graded treadmill testing. Patients ranged in age from 14 to 69 years (mean 47). There were 37 men and 33 women. All had echocardiographic confirmation of a hypertrophied, nondilated left ventricle in the absence of another cardiac or systemic disease capable of producing myocardial hypertrophy. 10, 11 Disproportionate septal thickening was present in 67 patients (96%). Cardiac catheterization in 68 patients demonstrated obstruction of the left ventricular outflow tract at rest (gradient of ≥ 30 mm Hg) in 25 patients (37%), a provokable outflow gradient during valsalva maneuver, amyl nitrite inhalation, or intravenous infusion of isoproterenol in 27 patients (40%), and no rest or provokable gradient in 16 patients (23%). The two patients not catheterized manifested marked systolic anterior motion of the anterior mitral valve on M mode echocardiography, compatible with the presence of a resting outflow gradient. All patients were limited by moderate-to-severe symptoms of angina, exertional dyspnea, orthopnea, or paroxysmal nocturnal dyspnea (New York Heart Association functional class III to IV). All patients were in normal sinus rhythm.

Short-term administration of verapamil. Fifty-five of the 70 patients were studied before and after short-term therapy with verapamil of 5 to 25 days (mean 9). In 28 patients verapamil was administered in a randomized, double-blind, cross-over manner at least 48 hr after cessation of all cardiac drugs. Verapamil (80 mg) or placebo were given every 6 hr. After nine low-dose capsules of the drug, high-dose capsules (120 mg) were administered every 6 to 8 hr for 48 hr and radionuclide angiography and graded exercise testing were performed. Two patients were studied during low-dose verapamil, since heart rate or blood pressure effects prevented high-dose administration. Fifteen of the 28 patients received placebo before verapamil, and the other 13 received verapamil before placebo. Results obtained during the placebo phase were considered “control” data for subsequent comparison with the effects of verapamil.

In the other 27 patients, verapamil was administered in an unblinded manner. Control studies were performed after cardiac medications were withdrawn for at least 48 hr. Verapamil was then administered orally, beginning at a dose of 240 or 320 mg/d. The dose was increased gradually every 36 to 48 hr as possible to a dose of 480 to 640 mg/d. The final dosage was determined by the clinical response of each patient and was limited in some patients because of atioventricular dissociation, Mobitz I second-degree atioventricular block, or systemic hypotension. Radionuclide angiography and graded treadmill testing were repeated after each patient received what was considered the optimal dose for at least 36 hr.

For the 55 patients undergoing short-term studies, the final daily verapamil dose was 240 mg in two patients, 320 mg in 14 patients, 360 mg in 16 patients, 480 mg in 22 patients, and 640 mg in one patient. Radionuclide angiography and exercise testing were performed within 1 week of verapamil initiation in 40 patients and within 8 to 25 days in the other 15 patients.

Long-term administration of verapamil. Twenty-five of the 70 patients were studied before and after long-term therapy of 1 to 2 years (mean 15 months). Drug dosage ranged from 320 to 640 mg/d. Eighteen of these patients were also included in the short-term study, so that serial control, short-term verapamil, and long-term verapamil data were obtained in these 18 patients. In 11 of these 18 patients, drug dosage was the same during the short- and long-term studies. In one patient the dose of verapamil was decreased from 480 to 320 mg/d between 1 week and 1 year; in the other six, increases in dosage were made during the course of the 1 to 2 year period because of persistent or progressive symptoms, from a median dose of 320 to 480 mg/d.

Verapamil withdrawal. We also studied the effects of verapamil withdrawal on left ventricular function and exercise performance in 24 patients after long-term verapamil therapy was complete. Sixteen of these patients were among the 25 patients in the long-term verapamil study, and the other eight patients were studied after long-term therapy but did not undergo initial control testing before verapamil treatment was begun. In these 24 patients, verapamil was discontinued after the long-term radionuclide angiographic and exercise tests were completed. The studies were then repeated 48 to 96 hr (mean 64) after verapamil was discontinued.

Gated equilibrium blood pool cardiac scintigraphy. Radionuclide angiography was performed at rest with red blood cells labeled in vivo with 15 to 20 mCi of technetium-99m. Imaging was performed with patients in the supine position by means of 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 from other cardiac structures. The cardiac image sequence spanning the average cardiac cycle was constructed from several hundred cardiac cycles by computer-based electrocardiographic gating, using list-mode data acquisition (framing rate up to 100 images/sec) with exclusion of extrasystolic and postextrasystolic cardiac cycles and combined forward and reverse gating from the R wave. 12 High temporal resolution left ventricular time-activity curves, representing a measure of relative left ventricular volume changes with time throughout the average cardiac cycle, were generated from the cardiac image sequence with use of fixed left ventricular and background regions of interest. 2, 3, 12 Left ventricular ejection fraction was determined automatically by computer analysis of the time-activity curve. The peak rates of left ventricular ejection and rapid diastolic filling were computed by fitting third-order polynomial functions to the systolic ejection phase and the rapid filling phase of the time-activity curve, with use of a least-squares technique. 3, 13 Peak ejection and filling rates were computed in counts per second, normalized for the number of counts at end-diastole and expressed as relative end-diatolic volumes per second (EDV/sec). Time to peak filling rate was computed as the time difference between end-systole (nadir of the time-activity curve) and the time corresponding to peak rate of filling. The reproducibility limits of these measurements in patients with hypertrophic cardiomyopathy have been reported previously. 2, 3 A change in peak filling rate of 0.4 EDV/sec (± 2 SDs) or greater was considered to be a significant change from baseline values.

In 34 patients studied during short-term administration of verapamil, we also performed radionuclide angiography during maximum supine exercise both before and after verapamil, with a bicycle ergometer and a restraining harness to minimize patient motion under the camera. Exercise loads were increased by 25 W every 2 min until the development of angina or limiting fatigue or dyspnea. Heart rate and blood pressure were monitored during exercise. Imaging was begun shortly after the onset of exercise, but only that portion of the data series that occurred during maximal exercise, encompassing approximately the last 2 to 3 min of exercise, was selected for analysis.

Graded treadmill exercise testing. Two different graded treadmill protocols, requiring different intensities of exercise, were used in this study to evaluate exercise capacity. 6, 7 The selection of the specific protocol used for each patient was a clinical decision based on age, sex, severity of symptoms, and expected exercise tolerance, with the goal that a symptomatic endpoint would be reached within 2.5 to 12.5 min of exercise. In the protocol requiring less intense exercise (protocol I), the treadmill was driven at a constant speed of 2.2 mph at an inclination of 0%. Every 2.5 min the inclination was increased by 2.5% until a maximum of 22.5 min elapsed. The maximum
workload at this final stage was 2.2 mph at 20% incline. In the more intense exercise protocol (protocol II), the treadmill was driven initially at 1.9 mph at an inclination of 10%. Every 2.5 min the treadmill speed and inclination were increased by 0.4 mph and 2%, respectively. After 15 min the inclination was held constant at 20% and the speed was increased 0.8 mph every 2.5 min. Exercise tolerance was assessed by protocol II in 59 of the 70 patients and protocol I in the other 11 patients. Subsequent exercise tests in the same patient were always performed with the same exercise protocol used in the initial study. In either protocol, exercise was terminated when the patient complained of angina, lightheadness, or limiting fatigue or dyspnea. No patient was forced to discontinue exercise because of the development of ventricular tachycardia.

To determine the reproducibility of exercise testing in patients with hypertrophic cardiomyopathy, exercise tolerance in 19 patients was studied twice during administration of placebo, at least 48 hr apart. The standard deviation of the mean difference (±11 sec) in exercise capacity between the two tests was 50 sec. Hence, a change in exercise capacity greater than 2 SDs (±100 sec) was considered a significant change compared with baseline values.

Echocardiography. M mode echocardiograms were obtained with a 2.25 MHz, 1.25 cm diameter, unfocused Aerotech transducer and a Hoffr st 101 ultrasonic receiver interfaced with a Honeywell 1856 strip-chart recorder or an Irex System II ultrasound unit with either a 2.25 or 3.5 MHz transducer (1.3 cm diameter). Ventricular septal and posterior left ventricular free wall thicknesses were measured before atrial systole with the ultrasound beam directed through the distal margins of the mitral leaflets.

Systolic anterior motion of the mitral valve was assessed with a semiquantitative grading system that was modified from that of Gilbert et al. Systolic anterior motion was defined as minimal if the minimum mitral-septal distance exceeded 10 mm, mild if this distance was 10 mm or less but there was no mitral-septal contact, moderate if there was only brief mitral septal contact (less than 30% of echocardiographic systolic ventricular systole), and severe if there was prolonged (30% or more of echocardiographic systolic ventricular systole) mitral-septal contact. These studies were interpreted by an experienced observer who was unaware of the results of radionuclide angiographic and exercise testing. Serial echocardiographic studies corresponding temporally to the serial radionuclide angiographic and graded exercise tests were obtained in 47 of the 62 patients studied before and after verapamil.

Statistical methods. The effects of verapamil on indexes of left ventricular function and exercise tolerance were analyzed with the paired t test. Serial studies obtained in patients under control conditions, during short-term therapy with verapamil, and during long-term therapy with verapamil were evaluated by analysis of variance of repeated measures. The relationship between changes in left ventricular diastolic filling and changes in exercise tolerance were assessed by linear regression analysis, chi-square analysis, and analysis of variance.

Results

Effects of short-term therapy with verapamil. During short-term administration of verapamil (table 1), indexes of left ventricular systolic function were unchanged compared with control values. However, as previously reported, indexes of left ventricular diastolic filling at rest significantly improved: peak filling rate increased and time to peak filling decreased, despite the reduction in heart rate (which would be expected to reduce peak filling rate and prolong time to peak filling rate). Peak filling rate increased (figure 1) from 3.1 ± 1.3 EDV/sec (mean ± SD) under control conditions to 3.7 ± 1.3 EDV/sec with verapamil (p < .001). Forty-three of the 55 patients manifested an increase in peak filling rate of 0.4 EDV/sec or greater, a change considered meaningfully greater than the control value.

Verapamil increased exercise capacity significantly (figure 1) from 5.9 ± 3.6 min under control conditions to 8.7 ± 4.7 min (p < .001). Exercise time increased by greater than 100 sec in 35 patients (64%). The magnitude of the change in exercise tolerance was associated with the change in peak filling rate. Exercise capacity improved significantly in the 43 patients manifesting an increase in peak filling rate after verapamil (figure 2), from 6.1 ± 3.8 to 9.6 ± 4.7 min (p < .001). However, in the 12 patients in whom peak filling rate was unchanged or decreased after verapamil, exercise capacity was not substantially altered (from 5.2 ± 2.7 to 5.7 ± 3.2 min; p = NS). Representative left ventricular time-activity curves are shown in figure 3 for a patient in whom improved left ventricular diastolic filling with verapamil was associated with increased exercise tolerance and for a patient in whom neither diastolic filling nor exercise tolerance increased with verapamil.

In the subset of 28 patients who received verapamil in a randomized, double-blind fashion, the results of short-term administration of verapamil were similar to those of the total group. Verapamil increased both resting peak filling rate (from 3.1 ± 1.2 to 3.8 ± 1.3 EDV/sec; p < .005) and exercise tolerance (from 5.3
crease in heart rate, there was a significant increase in peak filling rate (from $6.4 \pm 1.8$ to $7.1 \pm 1.9$ EDV/sec; $p < .02$) and a decrease in time to peak filling rate (from $130 \pm 40$ to $113 \pm 30$ msec; $p < .005$). As in the data obtained at rest, there was a significant association between increased peak filling rate during exercise and exercise tolerance. Fifteen of 18 patients with an increase in exercise peak filling rate manifested an increase in exercise tolerance compared with only seven of 16 patients in whom exercise peak filling rate was unchanged or decreased ($p < .02$ by chi-square analysis). An example of improved left ventricular filling at rest and during exercise after verapamil is presented in figure 4.

**Effects of long-term therapy with verapamil.** Serial data obtained in the 18 patients studied before and after both short- and long-term administration of verapamil demonstrated that the initial increase in resting peak filling rate during short-term therapy declined in most patients over the course of 1 to 2 years (figure 5), so

![FIGURE 1. Effects of short-term therapy with verapamil (1 to 4 weeks) on peak left ventricular (LV) filling rate at rest and on exercise capacity. Open circles with lines indicate mean values.](image)

- $3.1 \pm 8.5 \pm 4.3 \text{ min; } p < .001$). Exercise time was greater with verapamil than with placebo in 12 of 15 patients who received verapamil after placebo and in 10 of 13 patients who received verapamil before placebo. Hence the improvement in exercise time by verapamil could not be attributed purely to a training effect. In the 21 patients in whom peak filling rate increased after verapamil, exercise tolerance increased significantly (from $5.4 \pm 3.4$ to $9.4 \pm 4.5 \text{ min; } p < .001$), whereas exercise time was not altered (from $5.1 \pm 2.2$ to $5.7 \pm 2.3 \text{ min}$) in the seven patients in whom peak filling rate was decreased or unchanged after verapamil.

Similar data were obtained in the 34 patients who were studied by radionuclide angiography during exercise before and after short-term therapy with verapamil. Verapamil did not alter ejection fraction during exercise (from $71 \pm 9\%$ to $71 \pm 9\%$) but significantly decreased exercise heart rate (from $123 \pm 13$ to $113 \pm 2 \text{ beats/min; } p < .001$). Despite the significant de-
FIGURE 3. Left ventricular time-activity curves obtained at rest from two patients before (control) and after 1 week of orally administered verapamil. Each point represents 20 msec. Left, Improved peak filling rate after verapamil (from 1.9 to 3.4 EDV/sec) is associated with increased exercise capacity from 1.9 to 5.8 min. Right, Lack of increase in peak filling rate by verapamil (from 2.9 to 2.2 EDV/sec) is associated with no improvement in exercise tolerance.

FIGURE 4. Left ventricular time-activity curves obtained in one patient at rest and during exercise before and after verapamil. Despite increases in cardiac cycle length, verapamil increases peak filling rate both at rest (from 2.5 to 4.0 EDV/sec) and during exercise (from 5.7 to 7.1 EDV/sec) and is associated with a decrease in time to peak filling rate at rest (from 184 to 149 msec) and exercise (from 123 to 75 msec). Verapamil augmented exercise tolerance in this patient from 3.0 to 5.6 min.
that the mean value was significantly lower at 1 to 2 years than that measured at 1 to 4 weeks and was not significantly changed from the initial control value. Nonetheless, 10 patients (56%) still exhibited an increase in peak filling rate of 0.4 EDV/sec compared with control values. In similar fashion, exercise capacity, which increased in the majority of patients during short-term therapy, was only slightly greater than control values at 1 to 2 years of therapy. Nonetheless, exercise capacity at 1 to 2 years of therapy remained significantly greater than control and in nine patients (50%) was greater than 100 sec compared with control values.

Similar long-term results were evident when all 25 patients studied before and after long-term treatment were considered (table 2). Left ventricular systolic function was not altered by long-term therapy with verapamil. As with the short-term effects, however, resting peak filling rate was significantly greater than control values, and 16 patients (64%) had a persistent increase in peak filling rate of greater than 0.4 EDV/sec. Exercise capacity after long-term drug administration remained significantly longer than control values; 12 patients (48%) manifested an increased exercise capacity of greater than 100 sec compared with control.

These long-term effects of verapamil on exercise capacity were associated significantly with the drug's long-term effects on left ventricular diastolic filling. Verapamil-induced changes in exercise tolerance after 1 to 2 years of therapy are presented in figure 6 for all 25 patients studied before and after long-term treatment with verapamil. The 16 patients with a persistent increase in resting peak filling rate after 1 to 2 years of therapy manifested a significant increase in exercise tolerance over this period, from 6.8 ± 3.8 to 10.8 ± 3.9 min (p < .001). In contrast, in the nine patients with no change or a decrease in peak filling rate com-

**TABLE 2**

<table>
<thead>
<tr>
<th>Effect of long-term administration of verapamil (25 patients)</th>
<th>Control</th>
<th>Verapamil</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate at rest (beats/min)</td>
<td>79±20</td>
<td>68±11</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LV systolic function (rest)</td>
<td>71±11</td>
<td>71±11</td>
<td>NS</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>3.5±0.8</td>
<td>3.3±0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Peak LV ejection rate (EDV/sec)</td>
<td>369±52</td>
<td>366±43</td>
<td>NS</td>
</tr>
<tr>
<td>Time to end-systole (msec)</td>
<td>186±46</td>
<td>181±34</td>
<td>NS</td>
</tr>
<tr>
<td>LV diastolic filling (rest)</td>
<td>2.8±1.3</td>
<td>3.2±1.2</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Peak LV filling rate (EDV/sec)</td>
<td>1.4±0.4</td>
<td>1.5±0.5</td>
<td></td>
</tr>
<tr>
<td>Time to peak LV filling rate (msec)</td>
<td>186±46</td>
<td>181±34</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise capacity (min)</td>
<td>7.2±3.9</td>
<td>9.3±4.3</td>
<td>&lt;.02</td>
</tr>
</tbody>
</table>

Data are mean ± SD.

LV = left ventricular.
pared with initial control values, exercise tolerance at 1 to 2 years was unchanged from control values (from 7.8 ± 4.2 to 6.6 ± 3.6 min; p = NS).

**Change in diastolic filling vs change in exercise capacity.** The magnitude of the change in exercise capacity during treatment with verapamil and the influence of verapamil-induced changes in left ventricular diastolic filling on exercise tolerance were similar during both short- and long-term studies (figure 7). During both short- and long-term therapy, patients with an increase in resting peak filling rate compared with initial control values manifested a greater increase in exercise capacity than patients in whom peak filling rate was unchanged or decreased. Thirty-four of 43 patients (79%) with a verapamil-induced increase in peak filling rate during short-term therapy had an increase in exercise time greater than 100 sec relative to control values (table 3), compared with only one of 12 patients (8%) in whom peak filling rate was unchanged or decreased during short-term treatment with verapamil. The results were similar during long-term studies: 11 of 16 patients (69%) with a persistent increase in peak filling rate compared with initial control values manifested a persistent improvement in exercise tolerance, compared with only one of nine patients (11%) in whom peak filling rate was unchanged or decreased. By analysis of variance, the magnitude of the increase in peak filling rate was significantly related to the magnitude of change in exercise capacity during both short- and long-term studies (figure 8). Moreover, by linear regression analysis, a weak but significant correlation was observed between change in peak filling rate and change in exercise tolerance during short-term therapy (r = .38, p < .05); a stronger correlation was observed after long-term therapy (r = .60, p < .01).

**Echocardiographic data.** Among the 47 patients with serial echocardiographic data, 22 patients did not manifest significant mitral systolic anterior motion under basal conditions either before or during administration of verapamil. The remaining 25 patients had

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**FIGURE 6.** Effects of verapamil on exercise capacity during long-term therapy with verapamil (1 to 2 years). PFR = peak filling rate.

**FIGURE 7.** Change in exercise capacity compared with control values during short- and long-term therapy with verapamil. The change in exercise capacity is computed as the exercise time with verapamil minus the exercise time under control conditions. Patients are subdivided as in figures 2 and 6. PFR = peak filling rate.
systolic anterior motion before verapamil (moderate-to-severe in 23 and mild in two). In nine of these 25 patients, administration of verapamil resulted in a substantial reduction in the severity of mitral systolic anterior motion. In each of these nine patients, administration of verapamil resulted in both an increase in resting peak left ventricular filling rate and an improvement in exercise tolerance. Eleven of the other 16 patients with no reduction in severity of systolic anterior motion also manifested an increase in peak filling rate with verapamil. Thus verapamil increased peak filling rate in a total of 20 patients with systolic anterior motion, of whom nine (45%) demonstrated a concomitant reduction in the severity of systolic anterior motion. In comparison, none of the five patients in whom peak filling rate was unchanged or decreased with verapamil had a reduction in severity of systolic anterior motion.

**Effects of verapamil withdrawal.** Left ventricular systolic function was not altered by verapamil withdrawal after long-term therapy (table 4), but left ventricular diastolic filling significantly deteriorated: peak filling rate decreased significantly (figure 9), and time to peak filling rate increased. This was associated with a reduction in exercise capacity in 17 of the 24 patients (71%). However, this change in exercise tolerance for the group (from 8.5 ± 5.0 to 7.5 ± 5.2 min) did not achieve statistical significance.

**Discussion**

Relaxation and diastolic filling of the hypertrophied left ventricle are impaired in many patients with hypertrophic cardiomyopathy.1-4, 16-22 Prolonged or incomplete left ventricular relaxation and subsequent reduction in the rate and the extent of rapid filling result in reduced diastolic volume, reduced stroke volume, and altered diastolic pressure-volume relationships.16, 23-27 On the basis of these common physiologic abnormalities, it has been postulated, and generally accepted, that these abnormalities in left ventricular diastolic function contribute importantly to the clinical manifestations and severity of symptoms in patients with this disease.

The demonstration that verapamil and nifedipine improve indexes of left ventricular relaxation, filling, and diastolic distensibility1-4, 27-30 suggest that an im-

### TABLE 3
Verapamil-induced changes in diastolic filling and exercise capacity

<table>
<thead>
<tr>
<th>Verapamil effect on exercise capacity</th>
<th>Total No.</th>
<th>Increased ( ^a )</th>
<th>Unchanged or decreased</th>
<th>( p ) value( ^b )</th>
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</thead>
<tbody>
<tr>
<td>Short-term verapamil therapy</td>
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<td></td>
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<tr>
<td>Patients with increased PFR( ^c )</td>
<td>43</td>
<td>34 (79%)</td>
<td>9 (21%)</td>
<td>&lt; .001</td>
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<tr>
<td>Patients with unchanged or decreased PFR</td>
<td>12</td>
<td>1 (8%)</td>
<td>11 (92%)</td>
<td>( &lt; .02 )</td>
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<tr>
<td>Long-term verapamil therapy</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Patients with increased PFR( ^c )</td>
<td>16</td>
<td>11 (69%)</td>
<td>5 (31%)</td>
<td>( &lt; .2 )</td>
</tr>
<tr>
<td>Patients with unchanged or decreased PFR</td>
<td>9</td>
<td>1 (11%)</td>
<td>8 (89%)</td>
<td>( &lt; .2 )</td>
</tr>
</tbody>
</table>

\( \text{PFR} = \text{peak left ventricular filling rate at rest.} \)

\( ^a \)Increase defined as greater than 100 sec increase in exercise time compared with control values.

\( ^b \)Statistical significance by chi-square analysis.

\( ^c \)Increase defined as 0.4 EDV/sec or greater increase in peak filling rate compared with control values.

![FIGURE 8](image)

**FIGURE 8.** Change in exercise capacity with verapamil plotted as a function of the change in the resting left ventricular (LV) peak filling rate (PFR). *Top,* Short-term therapy; *bottom,* long-term therapy. Statistical significance computed by analysis of variance.
TABLE 4

<table>
<thead>
<tr>
<th>Effects of verapamil withdrawal (24 patients)</th>
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<tbody>
<tr>
<td>Verapamil</td>
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<tr>
<td>1–2 yr</td>
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<td>Verapamil withdrawal</td>
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<tr>
<td>p value</td>
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<td>Heart rate at rest (beats/min)</td>
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<td>LV systolic function (rest)</td>
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<td>LV ejection fraction (%)</td>
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<td>Peak LV ejection rate (EDV/sec)</td>
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<td>Time to end-systole (msec)</td>
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<tr>
<td>LV diastolic filling (rest)</td>
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<tr>
<td>Peak LV filling rate (EDV/sec)</td>
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<tr>
<td>Time to peak LV filling rate (msec)</td>
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<tr>
<td>Exercise capacity (min)</td>
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<tr>
<td>LV = left ventricular.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Verapamil</th>
<th>Verapamil</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate at rest</td>
<td>64 ± 10</td>
<td>74 ± 12</td>
<td>&lt; .001</td>
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<tr>
<td>LV systolic function</td>
<td>72 ± 7</td>
<td>73 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>3.4 ± 0.6</td>
<td>3.5 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Peak LV ejection rate</td>
<td>352 ± 32</td>
<td>348 ± 31</td>
<td>NS</td>
</tr>
<tr>
<td>Time to end-systole (msec)</td>
<td>181 ± 40</td>
<td>195 ± 44</td>
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<tr>
<td>Exercise capacity (min)</td>
<td>8.5 ± 4.9</td>
<td>7.5 ± 5.2</td>
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</table>

Important mechanism for the salutary clinical effects of the calcium channel-blocking agents in patients with hypertrophic cardiomyopathy is enhanced left ventricular diastolic function. The significant relationship in this study between improved rapid diastolic filling during therapy with verapamil and clinical improvement, measured objectively by exercise testing, supports this concept. Our data demonstrate that verapamil-induced improvement in left ventricular diastolic filling in patients with hypertrophic cardiomyopathy is associated with increased exercise capacity during both short- and long-term oral therapy.

In many of the patients in this study, it was not possible to exclude with certainty the possible contribution of a training effect with regard to the apparent improvement in exercise capacity by verapamil. However, several arguments suggest that potential training effects, if present, did not influence the exercise data importantly. First, in the 19 patients who exercised twice during the placebo phase, separated by at least 48 hr, to determine exercise reproducibility, the mean change between the first and second study was −11 sec, with 11 patients manifesting a decrease in exercise time during the second study compared with the first. Second, 28 of the 55 patients studied during short-term therapy with verapamil received the drug in a randomized, double-blind, cross-over fashion, with verapamil administered to 13 patients before placebo. The relative numbers of patients experiencing improved exercise tolerance with verapamil were the same whether verapamil was administered first or second in this protocol. Regarding the significant relationship between exercise tolerance and improved diastolic filling after verapamil, patients with increased peak filling rate after verapamil were subject to the same potential training effects on exercise capacity during both short- and long-term therapy with verapamil as those patients in whom peak filling rate did not increase.

Data obtained in the patients who underwent serial studies (figure 5) indicate that the initial increase in peak filling rate after several weeks declined in most patients over the subsequent 1 to 2 years. Exercise capacity also decreased in over half of the patients between short- and long-term studies. This deterioration in left ventricular diastolic filling and exercise capacity during long-term drug administration occurred despite doses of verapamil that were the same or higher than the initial dosage. Hence, these serial data might indicate the development of tachyphylaxis or drug tolerance. However, the results obtained during verapamil withdrawal (table 4, figure 9) demonstrate persistent long-term, reversible verapamil effects. Both diastolic filling and exercise tolerance deteriorated further in the majority of patients when the drug was
discontinued after 1 to 2 years. These findings suggest that disease progression rather than drug tolerance occurred during the course of long-term therapy with verapamil and that verapamil continued to exert a beneficial effect on left ventricular diastolic filling.

Improved left ventricular relaxation and filling by verapamil, reported by several investigators,\textsuperscript{1-4} results from the complex interrelationship of several potential drug effects, including altered left ventricular loading conditions, increased coronary blood flow, and reduced ventricular ischemia, in addition to possible direct myocardial effects. Although the actual mechanism or mechanisms responsible for improved left ventricular relaxation and filling by verapamil are difficult to establish, the beneficial clinical effects of improved diastolic function in reducing symptoms and increasing exercise tolerance are more readily explained. Increased rate and extent of rapid diastolic filling after verapamil\textsuperscript{1-4} is associated with increased end-diastolic volume and stroke volume, with unchanged or reduced diastolic filling pressures.\textsuperscript{5, 8, 9, 27, 31} Thus improved forward stroke volume is achieved while elevated pulmonary venous pressures are reduced (or at least not increased). Moreover, because the magnitude of the left ventricular outflow tract gradient is influenced by left ventricular volume,\textsuperscript{32-34} enhanced left ventricular filling and increased ventricular volumes may reduce the outflow gradient, which has been reported after administration of verapamil.\textsuperscript{5, 27, 31} This may result in decreased systolic wall tension and reduced oxygen requirements, further alleviating symptoms. Although the echocardiographic data did not demonstrate a consistent verapamil-induced reduction in the degree of systolic anterior motion of the mitral valve (an estimate of the severity of the subaortic gradient), systolic anterior motion was markedly reduced or obliterated in over one-third of those patients manifesting systolic anterior motion before therapy with verapamil.

In this study, we used the peak rate of rapid diastolic filling as an index of left ventricular relaxation and filling. This index cannot be considered a pure measure of diastolic performance, since it may also be influenced by heart rate, left ventricular systolic function, left ventricular volume, and possibly myocardial thickness. There is no evidence that the verapamil-induced increase in peak filling rate we observed in this study resulted from changes in heart rate or systolic function. Changes in peak filling rate are directly related to changes in heart rate. Because the reduction in heart rate by verapamil would by itself be expected to decrease the peak filling rate, the observed increase in peak filling rate by verapamil could not be explained by changes in heart rate. Changes in peak filling rate measured by radionuclide angiography are also directly related to changes in ejection fraction.\textsuperscript{35} Oral therapy with verapamil does not alter indexes of left ventricular systolic function in hypertrophic cardiomyopathy.\textsuperscript{2, 9} although intravenous administration of verapamil may result in clinically measurable negative inotropic effects.\textsuperscript{27}

In the current study, ejection fraction was not changed by short- or long-term oral therapy with verapamil and therefore did not influence peak filling rate measurements importantly. The issue regarding the influence of changes in left ventricular volume on this index of diastolic function is more complex and difficult to resolve. Improved rapid diastolic filling after verapamil may result in increased end-diastolic volume.\textsuperscript{5, 9, 27} On the other hand, increased end-diastolic volume could, in itself, influence the measurement of peak filling rate, although this effect might be minimized by normalizing the filling rate value (in counts/sec) by end-diastolic volume (that is, end-diastolic counts), as was done in this study. In our previous experience with verapamil administered intravenously in the catheterization laboratory,\textsuperscript{27} the consistent increase in end-diastolic volume after verapamil was not associated uniformly with increased peak filling rate; peak filling rate increased only in those patients with enhanced left ventricular relaxation (reduction in the time constant of left ventricular pressure decline) or in one patient with a marked increase in pulmonary wedge pressure (implicating a greater driving pressure across the mitral valve in early diastole). Thus increases in end-diastolic volume alone may not necessarily alter the peak rate of diastolic filling when this index is normalized for end-diastolic volume. In the current study, we did not measure absolute ventricular volumes (a limitation of the radionuclide method) to investigate the possible relationship between enhanced peak filling rate and changes in end-diastolic volume. Previous experience with M mode echocardiography indicated no change in left ventricular dimensions after orally administered verapamil,\textsuperscript{2} which may represent the inability of echocardiographic measurements to estimate volumes adequately in the irregularly shaped left ventricular cavities of patients with hypertrophic cardiomyopathy rather than definite evidence against a verapamil effect on left ventricular volume. Similarly, orally administered verapamil has not altered left ventricular wall thickness by this technique after 1 year of treatment,\textsuperscript{7} indicating either lack of a verapamil effect on left ventricular mass or the inability of M mode
echocardiography to assess mass accurately because of the inhomogeneous nature of the severity of hypertrophy throughout the left ventricle.\(^{11}\)

Our data indicate a significant relationship between verapamil-induced changes in peak filling rate at rest and improvement in exercise tolerance. Similar findings were observed regarding changes in peak filling rate during exercise. However, all measurements of filling rate obtained during exercise must be interpreted with great caution because of two factors. First, at higher heart rates there is loss of the diastasis interval, so that the rapid diastolic filling period (a period of ventricular filling influenced by active relaxation) overlaps with atrial systole (during which the ventricle fills passively during atrial contraction). This is shown in figure 4, in which the volume curves at rest have a definite period of diastasis, which is lost during exercise. Hence, the ability to study the rapid diastolic filling period, as a reflection of active relaxation and filling (which might be influenced by calcium-channel blockers or other interventions), is lost during exercise because of the compounding effect of superimposed atrial systole.

Second, the direct relationship between heart rate and peak filling rate is more pronounced during exercise. Under resting conditions, changes in cardiac cycle length are buffered by changes in duration of the diastasis interval. However, during exercise to higher heart rates and loss of the diastasis interval, the buffering effect of diastasis is lost, so that the measurement of peak filling rate is more sensitive to fluctuations in heart rate. This has important implications in the measurement of peak filling rate during exercise in patients before and after verapamil because of the consistent reduction in heart rate during exercise after verapamil. In this regard, during short-term therapy with verapamil, the separation of patients with improved and unimproved exercise tolerance on the basis of an increase or a decrease or no change in peak filling rate during exercise was not as definite as that observed in the peak filling rate data at rest. This may reflect the increasing dependence of peak filling rate on heart rate during exercise, so that potential beneficial effects of verapamil on left ventricular filling are masked by the significant decreases in heart rate. Because of these considerations, we believe that the changes in indexes of left ventricular filling under resting conditions may be more reliable indicators of alterations in diastolic function than those measured during exercise.

In summary, our results demonstrate that the increased rate of left ventricular rapid diastolic filling, as an index of improvement in diastolic function, is closely linked to clinical response to verapamil therapy in patients with hypertrophic cardiomyopathy. Patients with increased rate of diastolic filling are likely to experience an increase in exercise tolerance, whereas patients with no improvement in diastolic filling rate are not. Although the peak filling rate may be altered by factors other than left ventricular relaxation and filling, in the absence of more definitive data demonstrating a causal role of changes in heart rate, systolic function, or left ventricular volume or mass in augmenting this index of diastolic function after verapamil, our findings provide further evidence that impaired relaxation and filling of the hypertrophied left ventricle contribute importantly to the severity of symptoms in patients with this disease. These data also support the concept that enhanced left ventricular diastolic filling is a mechanism leading to the clinical improvement experienced by many patients with hypertrophic cardiomyopathy during long-term therapy with verapamil.

References


Verapamil-induced improvement in left ventricular diastolic filling and increased exercise tolerance in patients with hypertrophic cardiomyopathy: short- and long-term effects.
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