Effects of Verapamil on Left Ventricular Systolic Function and Diastolic Filling in Patients with Hypertrophic Cardiomyopathy

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

SUMMARY Verapamil improves exercise capacity in patients with hypertrophic cardiomyopathy (HCM), but its mechanisms of action are unknown. We examined the effects of oral verapamil (320-480 mg/day) on resting left ventricular (LV) systolic and diastolic function in patients with HCM. High-temporal-resolution time-activity curves from gated technetium-99m radionuclide angiograms were analyzed before and after verapamil therapy in 40 patients, of whom 16 were also studied during propranolol therapy (80-960 mg/day). All but one patient had normal or supranormal systolic function, but 70% had evidence of diastolic dysfunction, defined as peak LV filling rate (PFR) < 2.5 end-diastolic volumes (EDV)/sec or time to PFR > 180 msec. Verapamil did not change LV ejection fraction, peak ejection rate or ejection time, but did increase PFR (control 3.3 ± 1.0 EDV/sec, verapamil 4.1 ± 1.1 EDV/sec; p < 0.001) and reduce time to PFR (control 187 ± 56 msec, verapamil 159 ± 34 msec; p < 0.001). Only 30% of patients had evidence of diastolic dysfunction during verapamil. In contrast, propranolol did not change LV ejection fraction, PFR or time to PFR, but did prolong ejection time and reduce peak ejection rate. Thus, LV diastolic filling is abnormal in a high percentage of patients with HCM, and verapamil normalizes or improves these abnormalities without altering systolic function. This mechanism may contribute to the clinical improvement of many HCM patients during verapamil therapy.

CHRONIC ADMINISTRATION of verapamil increases exercise tolerance and improves symptoms in many patients with hypertrophic cardiomyopathy.1,2 While the acute i.v. administration of verapamil decreases left ventricular outflow tract obstruction in patients with hypertrophic cardiomyopathy,3 the increase in exercise capacity does not necessarily correlate with the decrease in subvalvular gradient. Hence, although a diminution in obstruction might contribute to the improved symptomatic status experienced by many patients on verapamil, other factors must also be involved.

In addition to subaortic obstruction, patients with hypertrophic cardiomyopathy manifest increased left ventricular contractility4,5 and impaired diastolic filling.5,6 The effect of verapamil on the hypercontractile left ventricle of hypertrophic cardiomyopathy is not known. Recent studies using M-mode echocardiography have demonstrated shortening of the isovolumic relaxation time and increase in the regional left ventricular filling rate after i.v. verapamil in patients with hypertrophic cardiomyopathy.10 The effect of chronic oral verapamil therapy on global left ventricular filling, however, has not been established.

In the current study, we analyzed high-temporal-resolution time-activity curves from gated technetium-99m radionuclide cineangiograms in patients with hypertrophic cardiomyopathy to determine the prevalence of abnormalities in left ventricular diastolic filling, and to assess the effects of oral verapamil on left ventricular systolic function and diastolic filling. The effects of oral propranolol were compared to those of verapamil in a subgroup of patients.

Methods

Patient Selection

We evaluated 40 patients, ages 15-69 years, admitted to the National Heart, Lung, and Blood Institute for evaluation of hypertrophic cardiomyopathy. The diagnosis of hypertrophic cardiomyopathy was based in all patients on echocardiographic demonstration of a hypertrophied, nondilated left ventricle in the absence of other acquired or congenital heart disease.11 Thirty-eight of 40 patients (95%) had disproportionate septal thickening with respect to the left ventricular free wall (septal-to-free wall ratio ≥ 1.3). In the other two patients, two-dimensional echocardiographic studies demonstrated regional disproportionate hypertrophy in the posterior septum or anterolateral free wall of the left ventricle in areas not traversed by the M-mode ultrasound beam. Left-heart catheterization studies in 34 of 40 patients (85%) demonstrated left ventricular outflow tract obstruction (basal or provoked gradient ≥ 30 mm Hg) in 30 patients (88%). Twenty of these patients were non-obstructive (gradient < 30 mm Hg) under basal conditions. Five of the six patients not catheterized had systolic anterior motion of the anterior mitral valve leaflet at rest demonstrated by echocardiography.

All patients were functionally limited at the time of admission. Thirty-four were in New York Heart...
Association functional class III and six were in class II. Thirty-five patients were receiving propranolol at the time of admission (80–960 mg/day). The other patients had taken propranolol previously, but it was discontinued because of side effects (three patients) or progressive symptoms (two patients). Thirty-two patients complained of chest pain, 36 of exertional dyspnea, and 31 of presyncope. Thirteen patients had a history of syncope.

Drug Administration

Radionuclide cineangiographic and M-mode echocardiographic studies were performed at least 48 hours after the cessation of propranolol and all other cardiac medications except for diuretics. Blood pressure and heart rate were measured in the supine position at the time of radionuclide study. After the control measurements, oral verapamil therapy was initiated at a dose of 240 mg daily in divided doses. The dose of verapamil was gradually increased every 48 hours to a maximum of 360–480 mg daily. The verapamil dose was either not increased or was decreased if there was evidence of atioventricular dissociation, Mobitz I second-degree atioventricular block, or systemic hypotension. The final verapamil dosage was tailored to fit the individual clinical setting of each patient. The final dose of verapamil ranged from 320–480 mg daily (mean 380 mg). After each patient received what was considered to be the optimal verapamil dosage for at least 36 hours, radionuclide studies and measurements were repeated. Repeat echocardiographic studies were performed during verapamil administration in 21 patients. In addition to the radionuclide studies performed under control conditions and during verapamil therapy, 16 of the 40 patients (40%) underwent radionuclide cineangiography shortly after admission while still receiving propranolol, 80–960 mg daily (mean 240 mg).

Radionuclide Cineangiography

Gated equilibrium blood pool cardiac scintigraphy was performed at rest 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) that spanned the average cardiac cycle and 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. Blood radioactivity is proportional to blood volume, so after background correction, the time-activity curve represents a measure of relative left ventricular volume changes with time.

Left ventricular ejection fraction at rest was determined by computer analysis of the time-activity curves. Peak left ventricular ejection rate and filling rate were then computed as previously described, by fitting a third-degree polynomial function to the systolic ejection and rapid diastolic filling portions of the time-activity curve, 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 at rest. These were left ventricular ejection fraction, peak left ventricular ejection rate, and left ventricular ejection time (measured from the R wave to end-systole). Variables used to express left ventricular diastolic filling were peak left ventricular filling rate and time to peak filling rate. The validity of determining these variables from gated time-activity curves has been described.

The reproducibility of the variables describing left ventricular systolic function and diastolic filling in patients with hypertrophic cardiomyopathy was determined in 12 other patients. The diagnosis of hypertrophic cardiomyopathy was established in each patient by M-mode echocardiographic criteria. Each patient had a septal-to-free wall ratio of greater than 1.3. Two radionuclide cineangiographic studies were performed after a single injection of technetium-99m, separated by at least 4 hours, during which time the patient was ambulatory and received no medications. The initial radionuclide study was performed at least 48 hours after the cessation of all cardiac medications.

Normal values of the variables describing left ventricular systolic function and diastolic filling, determined in 45 normal volunteers, have been reported and are presented in Table 1. These normal volunteers, ages 21–63 years, had no cardiac symptoms and had normal physical examinations, chest x-rays, ECGs and echocardiograms.

Statistical Methods

Data were analyzed by the t test, using unpaired and paired data as appropriate, and by linear regression analysis.
TABLE 1. Variables Describing Left Ventricular Systolic Function and Diastolic Filling

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects* (n = 45)</th>
<th>Hypertrophic (n = 40)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Mean ± SD</td>
<td>Range</td>
</tr>
<tr>
<td>LV systolic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>45-72</td>
<td>55 ± 6</td>
<td>44-96</td>
</tr>
<tr>
<td>Peak LV ejection rate (EDV/sec)</td>
<td>1.9-3.7</td>
<td>2.7 ± 0.5</td>
<td>2.5-5.7</td>
</tr>
<tr>
<td>LV ejection time (msec)</td>
<td>260-450</td>
<td>344 ± 33</td>
<td>290-500</td>
</tr>
<tr>
<td>LV diastolic filling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak LV filling rate (EDV/sec)</td>
<td>2.5-5.0</td>
<td>3.3 ± 0.6</td>
<td>1.7-6.2</td>
</tr>
<tr>
<td>Time to peak filling rate (msec)</td>
<td>90-180</td>
<td>136 ± 23</td>
<td>100-380</td>
</tr>
</tbody>
</table>

Abbreviations: EDV = end diastolic volume; LV = left ventricular.

*The data obtained from the 45 normal subjects has been reported in detail.15

Results

Normal Volunteers

The data from the 45 normal volunteers are presented in table 1. The 99% confidence limits for the normal data have been determined to define the lower limit of normal for peak filling rate (2.5 EDV/sec) and the upper limit of normal for time to peak filling rate (180 msec). Time to peak left ventricular filling rate did not correlate with the peak filling rate (r = 0.26, fig. 1). Peak left ventricular filling rate and time to peak filling rate also did not correlate with heart rate, age or echocardiographic left ventricular end-diastolic dimension. Peak filling rate correlated significantly with left ventricular ejection fraction, but with a low correlation coefficient (r = 0.51, p < 0.001).18

Patients with Hypertrophic Cardiomyopathy

Control Measurements

Left ventricular systolic function. Left ventricular ejection fraction in the 40 patients with hypertrophic cardiomyopathy was significantly greater than normal (p < 0.001, table 1). Ejection fraction was subnormal (less than 45%) in one patient and was greater than 72%, the highest value measured in the normal volunteers, in 26 of the 40 patients (65%). Peak left ventricular ejection rate was also greater than normal (p < 0.001). Left ventricular ejection time was not different from normal. Only three patients exceeded an ejection time of 450 msec, the longest value recorded in the normal persons.

Left ventricular diastolic filling. Peak left ventricular filling rate in the patients with hypertrophic cardiomyopathy was not significantly different from normal for the group as a whole (table 1), although 10 of 40 patients (25%) manifested peak filling rates less than 2.5 EDV/sec, the lower limit of normal (fig. 1). Time to peak filling rate was prolonged compared with normal subjects (p < 0.001, table 1). The time to peak filling rate exceeded the upper limit of normal (180 msec) in 21 (53%) of the 40 patients (fig. 1). Peak filling rate did not correlate with time to peak filling rate (r = 0.27), so both variables were used as in-

![Figure 1. Peak left ventricular (LV) filling rate plotted as a function of time to peak filling rate for 45 normal volunteers and 40 patients with hypertrophic cardiomyopathy (HCM). The dashed lines indicate the lower limit of normal (99% confidence limits) for peak filling rate (2.5 end-diastolic volumes [EDV]/sec) and upper limit of normal for time to peak filling rate (180 msec).](http://circ.ahajournals.org/)
diomyopathy. As beats/min).

Only 12 patients (30%) fell within the normal range defined by peak left ventricular filling rate of 2.5 EDV/sec or greater and a time to peak filling rate of 180 msec or less (fig. 1). Of 28 patients with abnormal left ventricular diastolic filling, seven patients had subnormal peak filling rates but normal times to peak filling rate, 18 had normal peak filling rates but prolonged times to peak filling rate, and three had subnormal peak filling rates and prolonged times to peak filling rate. Figure 2 shows an example of abnormal diastolic filling in a patient with hypertrophic cardiomyopathy.

Resting heart rates were not different between patients with hypertrophic cardiomyopathy (78 ± 17 beats/min) and the normal volunteers (78 ± 15 beats/min). As in the normal volunteers, the peak left ventricular filling rate and time to peak filling rate in the patients with hypertrophic cardiomyopathy did not correlate with age (r = -0.29; r = -0.07), heart rate (r = 0.16; r = -0.16), ejection time (r = -0.11; r = -0.05), echocardiographic left ventricular end-diastolic dimension (r = 0.023; r = -0.11), end-systolic dimension (r = 0.16; r = 0.22), or (in the patients who underwent left-heart catheterization) left ventricular end-diastolic pressure (r = 0.13; r = 0.03). The left ventricular diastolic filling variables in the patients with hypertrophic cardiomyopathy also did not correlate with left ventricular ejection fraction (r = -0.29; r = -0.05) (fig. 3).

Figure 2. Unretouched time-activity curves from a 22-year-old normal volunteer and a 16-year-old patient with hypertrophic cardiomyopathy (HCM). (B) Schematic representations of the two curves. The patient with HCM has similar heart rate (74 vs 78 beats/min), ejection fraction (67 vs 65%) and ejection time (340 vs 320 msec) compared with the normal volunteer. However, in the patient with HCM, peak filling rate is diminished (2.2 vs 3.6 EDV/sec) and time to peak filling rate (TPFR) is prolonged (198 vs 155 msec). EDV = end-diastolic volume.

Effect of Verapamil

Resting heart rate decreased during verapamil therapy (table 2, fig. 4) from a control of 78 ± 17 to 68 ± 10 beats/min (p < 0.001). Heart rate increased in nine patients, did not change in two patients, and decreased in the remaining 29 patients (73%). Neither systolic and diastolic blood pressure, measured in the supine position at the time of the radionuclide study, nor echocardiographic left ventricular diastolic and systolic dimensions changed during verapamil compared with control values.

Left ventricular systolic function. Left ventricular ejection fraction, peak left ventricular ejection rate, and left ventricular ejection time were unaltered by verapamil (table 2, fig. 4). Both left ventricular ejection fraction and peak left ventricular ejection rate remained higher than normal (p < 0.001) during verapamil.

Left ventricular diastolic filling. Peak left ventricular filling rate significantly increased (table 2, fig. 5) during verapamil therapy (p < 0.001). Peak filling rate decreased in four patients (these patients had four of the five highest levels of peak filling rate before verapamil), did not change in one patient, and increased in the 35 other patients (88%). Only two patients (5%) had subnormal peak filling rates (less than 2.5 EDV/sec) during verapamil therapy (table 3). All four patients whose peak filling rate decreased during verapamil had prolonged times to peak filling rate before verapamil (fig. 6A); each had a reduction in
VERAPAMIL AND LV FILLING IN HCM/Bonow et al.

![Graph A](image)

**FIGURE 3.** Peak left ventricular (LV) filling rate (A) and time to peak LV filling rate (B) plotted as functions of LV ejection fraction for the normal volunteers and patients with hypertrophic cardiomyopathy (HCM). Symbols are explained in figure 1.

Time to peak filling rate during verapamil (234 ± 72 msec during control and 169 ± 38 msec during verapamil; p < 0.05). Time to peak filling rate also diminished during verapamil (table 2, fig. 6B) for the entire group of 40 patients (187 ± 56 msec during control and 159 ± 34 msec during verapamil; p < 0.001).

Time to peak filling rate increased in six patients, did not change in three patients, and decreased in the remaining 31 patients (78%). Prolonged time to peak filling rate (greater than 180 msec) was observed in only 10 patients (25%) during verapamil therapy (table 3).

Hence, noninvasive evidence for improved left ventricular diastolic filling (both an increase in peak filling rate, and a reduction in time to peak filling rate) was observed in 30 of the 40 patients. Thirty-nine of the 40 patients manifested either an increase in peak filling rate or a decrease in time to peak filling rate or both. Abnormal diastolic filling (either a peak filling rate less than 2.5 EDV/sec, or a time to peak filling rate greater than 180 msec), present in 70% of patients before verapamil, was present in only 12 patients (30%) during verapamil (table 3). Examples of improved left ventricular diastolic filling during verapamil are illustrated in figure 7.

Two of the four patients whose peak filling rate decreased during verapamil therapy showed dramatic changes in the shape of the time-activity curves during verapamil. In these patients, ventricular filling under control conditions appeared to be accomplished predominantly during atrial systole (fig. 8), resulting in a high rate of filling at the end of the cardiac cycle. The contribution of rapid early diastolic filling to ventricular filling appeared negligible, and the early diastolic portion of the curve was flattened. During verapamil, ventricular filling occurred predominantly during the rapid diastolic filling phase of diastole, with less contribution from atrial systole. This resulted in a visual improvement in early diastolic filling of the time-activity curve despite an apparent reduction in peak left ventricular filling rate (fig. 8). This improvement in filling was reflected by a marked decrease in time to peak filling rate.

**TABLE 2. Effect of Verapamil in 40 Patients with Hypertrophic Cardiomyopathy**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Verapamil</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Mean ± SD</td>
<td>Range</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>46-126</td>
<td>78 ± 17</td>
<td>45-94</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>90-160</td>
<td>118 ± 18</td>
<td>80-150</td>
</tr>
<tr>
<td>Diastolic</td>
<td>50-95</td>
<td>67 ± 12</td>
<td>50-85</td>
</tr>
<tr>
<td>LV systolic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>44-96</td>
<td>75 ± 9</td>
<td>43-93</td>
</tr>
<tr>
<td>Peak LV ejection rate (EDV/sec)</td>
<td>2.5-5.7</td>
<td>3.7 ± 0.7</td>
<td>2.1-4.8</td>
</tr>
<tr>
<td>LV ejection time (msec)</td>
<td>290-500</td>
<td>360 ± 50</td>
<td>300-480</td>
</tr>
<tr>
<td>LV diastolic filling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak LV filling rate (EDV/sec)</td>
<td>1.7-6.2</td>
<td>3.3 ± 1.0</td>
<td>1.9-7.3</td>
</tr>
<tr>
<td>Time to peak filling rate (msec)</td>
<td>100-380</td>
<td>187 ± 56</td>
<td>70-224</td>
</tr>
<tr>
<td>Echocardiographic LV dimension (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-diastolic</td>
<td>31-50</td>
<td>39 ± 6</td>
<td>31-50</td>
</tr>
<tr>
<td>End-systolic</td>
<td>16-31</td>
<td>22 ± 4</td>
<td>14-31</td>
</tr>
</tbody>
</table>

Abbreviations: LV = left ventricular; EDV = end-diastolic volume.
In the subgroup of patients without left ventricular outflow tract obstruction under basal conditions, unequivocal evidence for improved left ventricular diastolic filling was observed in 14 of 20 patients. Nineteen of the 20 patients had either an increase in peak filling rate or a decrease in time to peak filling rate or both.

**Effect of Verapamil vs Effect of Propranolol**

In the subgroup of patients studied during propranolol therapy, heart rates were lower than control values during both propranolol and verapamil (table 4). Heart rates during propranolol (61 ± 12 beats/min), however, were not significantly different from those during verapamil (67 ± 8 beats/min). Systolic and diastolic blood pressures were the same during propranolol, verapamil and control conditions.

**Left Ventricular Systolic Function.** Left ventricular ejection fraction did not change during either medication (77 ± 9% for control, propranolol and verapamil). As in the larger group of 40 patients, neither peak ejection rate nor ejection time changed during verapamil. During propranolol, however, peak

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**TABLE 3. Effect of Verapamil on the Incidence of Diastolic Filling Abnormalities**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th></th>
<th>Verapamil</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Subnormal peak LV filling rate (&lt; 2.5 EDV/sec)</td>
<td>10</td>
<td>25%</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>Prolonged time to peak LV filling rate (&gt; 180 msec)</td>
<td>21</td>
<td>53%</td>
<td>10</td>
<td>25%</td>
</tr>
<tr>
<td>Either subnormal peak LV filling rate, prolonged time to peak filling rate, or both</td>
<td>28</td>
<td>70%</td>
<td>12</td>
<td>30%</td>
</tr>
</tbody>
</table>

Abbreviations: LV = left ventricular; EDV = end-diastolic volume.
ejection rate significantly decreased relative to control and verapamil levels and ejection time significantly increased (table 4).

**Left Ventricular Diastolic Filling.** In this subgroup of patients, the effects of verapamil were similar to those in the larger group of 40 patients. Thus, peak filling rate increased during verapamil \( p < 0.01 \) and time to peak filling rate decreased \( p < 0.001 \). Propranolol resulted in no change in either variable compared with control values (table 4). Hence, peak filling rate during verapamil was greater than during propranolol \( p < 0.001 \) and time to peak filling rate was shorter \( p < 0.005 \).

**Reproducibility of Radionuclide Measurements**

In the 12 patients who were studied two times while taking no cardiac medications, none of the variables describing left ventricular systolic function or diastolic filling demonstrated significant change during the two studies (table 5). The average change between studies was \( 0 \pm 3 \% \) for left ventricular ejection fraction, \( 0 \pm 0.2 \) EDV/sec for peak ejection rate, \( 4 \pm 11 \) msec for ejection time, \( 0 \pm 0.2 \) EDV/sec for peak filling rate, and \(-3 \pm 18 \) msec for time to peak filling rate. The maximum change in peak filling rate was 0.5 EDV/sec. The maximum change in time to peak filling rate was 35 msec.

**Discussion**

Abnormalities in diastolic properties of the left ventricle in patients with hypertrophic cardiomyopathy\(^6-9,17-22\) and other forms of left ventricular hypertrophy\(^13-25\) have been reported. Impaired isovolumic relaxation,\(^6-9,18\) diminished rapid diastolic filling rates,\(^6-9,17\) prolonged rapid diastolic filling periods,\(^6,7\) and increased chamber stiffness\(^6,19-20\) have been demonstrated using hemodynamic, contrast angiographic and echocardiographic techniques. In the current study, abnormal indexes of left ventricular diastolic filling, determined noninvasively by radionuclide ventriculography, were detected in 70% of the patients with hypertrophic cardiomyopathy. Fifty-three percent of these patients had a prolonged time to peak left ventricular filling rate (table 3). Twenty-five percent had subnormal peak filling rates. During oral verapamil therapy, 30 of 40

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**Figure 6.** Time to peak left ventricular (LV) filling rate before (control) and during verapamil therapy for the four patients whose peak filling rate decreased during verapamil (A) and for all 40 patients with hypertrophic cardiomyopathy (B). Slashed circles indicate mean values.

**Figure 7.** Unretouched time-activity curves from two patients before (control) and during verapamil therapy. Verapamil results in increased peak filling rate (1.9 to 3.4 end-diastolic volumes [EDV]/sec in patient A and 2.4 to 3.4 EDV/sec in patient B) and reduced time to peak filling rate (165 to 150 msec in patient A and 380 to 218 msec in patient B).
patients showed unequivocal improvement in left ventricular diastolic filling, manifested by both increased peak filling rates and decreased time to peak filling rates (table 2, figs. 5–8). In two other patients whose peak filling rate decreased during verapamil, inspection of the time-activity curves indicated unequivocal improvement in the rapid filling phase of diastole (fig. 8). Only 30% of the patients had abnormal diastolic filling indexes during verapamil, compared with 70% under control conditions (table 3).

Peak filling rate increased in 35 of 40 patients (88%), including 25 of 30 patients (83%) with “normal” peak filling rates under control conditions. We previously showed that peak filling rate is directly proportional to left ventricular ejection fraction for normal volunteers ($r = 0.51$, $p < 0.001$) and for patients with coronary artery disease ($r = 0.73$, $p < 0.001$). Hence, in many patients with hypertrophic cardiomyopathy, a condition in which ejection fraction is supranormal, a “normal” peak left ventricular filling rate may be diminished relative to left ventricular contractile function (fig. 3).

Without quantitative left ventricular volume measurements and analysis of simultaneous pressure-volume relations throughout diastole, the abnormalities of left ventricular diastolic filling and their improvement with verapamil cannot be attributed with certainty to abnormalities and changes in left ventricular compliance. Moreover, the mechanism by which verapamil reduces the time to peak filling rate cannot be determined without also determining the precise instant of mitral valve opening. Thus, diminution of a prolonged time to peak filling rate may result from shortening of the isovolumic relaxation time, shortening of the period of rapid filling, or shortening of both of these phases of diastole. Finally, in the absence of quantitative estimation of left ventricular volume, the peak left ventricular filling rates (a measure of rapid diastolic filling) cannot be expressed as changes in absolute volume, but only as changes relative to end-diastolic volume.

Other factors besides changes in left ventricular stiffness might account for the alterations we observed in relative left ventricular filling during verapamil. Blood pressure, absolute left ventricular volume at end-diastole and end-systole, and left atrial pressure are important loading variables that may alter relaxation and filling of the left ventricle. Neither systolic nor diastolic blood pressure, however, measured in the

**TABLE 4. Effect of Propranolol and of Verapamil in 16 Patients with Hypertrophic Cardiomyopathy**

<table>
<thead>
<tr>
<th></th>
<th>Control Range</th>
<th>Control Mean ± SD</th>
<th>Propranolol Range</th>
<th>Propranolol Mean ± SD</th>
<th>Verapamil Range</th>
<th>Verapamil Mean ± SD</th>
<th>Statistical difference between propranolol and verapamil</th>
<th>$p$</th>
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</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>62–106</td>
<td>79 ± 18</td>
<td>48–71</td>
<td>61 ± 12†</td>
<td>59–84</td>
<td>67 ± 8†</td>
<td>NS</td>
<td></td>
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<tr>
<td>Blood pressure (mm Hg)</td>
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<tr>
<td>Systolic</td>
<td>95–160</td>
<td>119 ± 16</td>
<td>90–160</td>
<td>115 ± 19</td>
<td>95–140</td>
<td>118 ± 11</td>
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<tr>
<td>Diastolic</td>
<td>50–95</td>
<td>66 ± 2</td>
<td>50–90</td>
<td>67 ± 10</td>
<td>50–80</td>
<td>68 ± 9</td>
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<tr>
<td>LV systolic function</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>67–90</td>
<td>77 ± 6</td>
<td>68–90</td>
<td>77 ± 6</td>
<td>67–93</td>
<td>77 ± 6</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Peak LV ejection rate (EDV/sec)</td>
<td>2.9–5.7</td>
<td>3.7 ± 0.7</td>
<td>2.6–5.3</td>
<td>3.4 ± 0.6†</td>
<td>2.7–4.8</td>
<td>3.8 ± 0.5</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>LV ejection time (msec)</td>
<td>300–460</td>
<td>364 ± 45</td>
<td>320–480</td>
<td>400 ± 48†</td>
<td>320–420</td>
<td>365 ± 28</td>
<td>&lt;0.005</td>
<td></td>
</tr>
<tr>
<td>LV diastolic filling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak LV filling rate (EDV/sec)</td>
<td>1.8–5.6</td>
<td>3.3 ± 1.0</td>
<td>1.5–4.5</td>
<td>3.1 ± 0.9</td>
<td>1.9–5.8</td>
<td>4.1 ± 0.9*</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Time to peak filling rate (msec)</td>
<td>141–339</td>
<td>200 ± 48</td>
<td>122–297</td>
<td>197 ± 49</td>
<td>112–224</td>
<td>164 ± 30†</td>
<td>&lt;0.005</td>
<td></td>
</tr>
</tbody>
</table>

Statistical difference compared with control:

* $p < 0.01$.
† $p < 0.001$.

Abbreviations: LV = left ventricular; EDV = end-diastolic volume.
supine position at the time of the radionuclide study, changed during verapamil. End-diastolic and end-systolic left ventricular volumes also probably did not change during verapamil, as deduced from M-mode echocardiographic measurements. While direct measurement of left atrial pressure was not obtained in these patients during oral verapamil therapy, previous data from our laboratory indicate that pulmonary artery wedge pressure does not usually change during i.v. verapamil infusion.

Left ventricular contractile function and heart rate also influence diastolic filling of the left ventricle. Verapamil did not appear to alter left ventricular contractility, as assessed by ejection fraction, peak ejection rate and ejection time, but did significantly reduce resting heart rate (table 2, fig. 4). However, this verapamil-induced reduction in heart rate is probably not responsible for the improvement in diastolic filling. Preliminary studies in our laboratory using atrial pacing have demonstrated that a reduction in heart rate is associated with a decrease in peak filling rate and a prolongation of time to peak filling rate (Bonow RO, Rising DR, Ostrow HG, Lipson LC, Kent KM, Bacharach SL, Green MV, Epstein SE: manuscript in preparation). Thus, verapamil resulted in an increased peak filling rate and a decreased time to peak filling rate in the current study despite a reduction in heart rate. Also, propranolol therapy resulted in an equally significant decrease in heart rate (table 4), but did not alter either peak filling rate or time to peak filling rate (despite a reduction in peak ejection rate and prolongation of ejection time).

The results of this study demonstrate that verapamil improves left ventricular diastolic filling in many patients with hypertrophic cardiomyopathy without altering systolic function. The improvement in global left ventricular filling during oral verapamil is consistent with the data of Hanrath et al., who detected improvement in left ventricular relaxation time and regional left ventricular filling (peak rate of posterior wall thinning) in patients with hypertrophic cardiomyopathy, using M-mode echocardiography 5–10 minutes after i.v. verapamil. Our data support the concept that improvement in diastolic filling of the left ventricle contributes to the clinical improvement of many patients with hypertrophic cardiomyopathy during chronic oral verapamil therapy.

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Cardiology 45: 141, 1980

Cardioprotective Effects of Lidoflazine During 1-hour Normothermic Global Ischemia

W. FLAMENG, M.D., W. DAINEN, M.D., M. BORGERS, DR. SC., F. THONE, R. XHONNEUX, A. VAN DE WATER, AND H. VAN BELLE

SUMMARY The cardioprotective effects of lidoflazine, a drug with calcium homeostatic properties, were investigated in dogs subjected to 1 hour of normothermic global ischemia, followed by reperfusion. None of the eight control dogs could be weaned from the extracorporeal bypass, confirming the severity of the ischemic model. All eight acutely pretreated dogs showed rapid recovery from the prolonged ischemic arrest and could support their own circulation. Recovery of preischemic values was 95% for systolic aortic pressure, 71% for diastolic aortic pressure, 99% for left ventricular dP/dt max and 80% for cardiac output. Light and electron microscopy and calcium cytochemistry were performed on left ventricular biopsies taken before, during and after ischemic arrest. In the control dogs, loss of structural integrity of the sarcolemma and mitochondria was prominent at the end of the ischemic period. Intracellular edema, hypercontraction of sarcomeres and great accumulation of calcium in severely damaged mitochondria occurred after 5 and 30 minutes of reperfusion. In the lidoflazine-treated dogs, such lesions were largely prevented during the ischemic period and completely reversed after reperfusion. These observations suggest that the tolerance to ischemia is markedly augmented by lidoflazine.

NAYLER1 suggested that lidoflazine exerts a protective effect on the ischemic and reperfused heart muscle. In the experiments on the isolated rabbit heart perfused by the Langendorff method, the drug was found to suppress the steep rise in end-diastolic contracture that takes place upon reoxygenation of the ischemic myocardium. The recovery of developed tension was found to be strongly enhanced in pretreated hearts. Mitochondrial functions, determined after measurements of oxidative phosphorylation, ATP generation and calcium content, which were drastically altered after prolonged ischemia and reperfusion, remained close to control values in the lidoflazine-pretreated hearts.

Lidoflazine (Clinium), 4-[4,4-bis(4, fluorophenyl) butyl]-N-[(2,6-dimethyl-phenyl)-1-piperazine acetamide, is known to be beneficial in the long-term treatment of ischemic heart disease and to enhance work tolerance in patients with angina pectoris.2-7 It has

From the Department of Cardiovascular Surgery, University of Leuven, Leuven, and Janssen Pharmaceutica Research Laboratories, Beerse, Belgium.
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Address for correspondence: W. Flameng, M.D., Department of Cardiovascular Surgery, University Clinic St. Rafael, Kapucijnenvoer 35, B-3000 Leuven, Belgium.
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