Effects of verapamil on left ventricular systolic and diastolic function in patients with hypertrophic cardiomyopathy: pressure-volume analysis with a nonimaging scintillation probe

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ABSTRACT To investigate the effects of verapamil on left ventricular systolic and diastolic function in patients with hypertrophic cardiomyopathy, we studied 14 patients at catheterization with a nonimaging scintillation probe before and after serial intravenous infusions of low-, medium-, and high-dose verapamil (total dose 0.17 to 0.72 mg/kg). Percent change in radionuclide stroke counts after verapamil correlated well with percent change in thermodilution stroke volume (r = .87), and changes in diastolic and systolic counts were used to assess relative changes in left ventricular volumes after verapamil. Verapamil produced dose-related increases in end-diastolic counts (19 ± 9% increase; p < .001), end-systolic counts (91 ± 74% increase; p < .001), and stroke counts (7 ± 10% increase; p < .02). This was associated with a decrease in ejection fraction (83 ± 8% control, 73 ± 10% verapamil; p < .001) and, in the 10 patients with left ventricular outflow tract gradients, a reduction in gradient (62 ± 27 mm Hg control, 32 ± 35 mm Hg verapamil; p < .01). The end-systolic pressure-volume relation was shifted downward and rightward in all patients, suggesting a negative inotropic effect. In 10 patients, left ventricular pressure-volume loops were constructed with simultaneous micromanometer pressure recordings and the radionuclide time-activity curve. In five patients, verapamil shifted the diastolic pressure-volume curve downward and rightward, demonstrating improved pressure-volume relations despite the negative inotropic effect, and also increased the peak rate of rapid diastolic filling. In the other five patients, the diastolic pressure-volume relation was unaltered by verapamil, and increased end-diastolic volumes occurred at higher end-diastolic pressures; in these patients, the peak rate of left ventricular diastolic filling was not changed by verapamil. The negative inotropic effects of intravenous verapamil are potentially beneficial in patients with hypertrophic cardiomyopathy by decreasing left ventricular contractile function and increasing left ventricular volume. Verapamil also enhances left ventricular diastolic filling and improves diastolic pressure-volume relations in some patients despite its negative inotropic effect.


VERAPAMIL THERAPY decreases symptoms and improves exercise capacity in many patients with hypertrophic cardiomyopathy.1,2 The hemodynamic mechanisms responsible for these beneficial clinical effects are incompletely understood. Previous studies have demonstrated that verapamil improves relaxation and early rapid diastolic filling of the hypertrophied left ventricle3,4 and, in patients with left ventricular outflow tract obstruction, reduces the subvalvular pressure gradient while cardiac output is unchanged or increases.5 To investigate the interrelation between improved left ventricular filling and reduced outflow obstruction and to further explore the relevant mechanisms for symptomatic improvement, we studied the hemodynamic effects of verapamil in 14 patients with hypertrophic cardiomyopathy during cardiac catheterization by means of an electrocardiogram (ECG)-gated nonimaging scintillation probe system.

Methods

Patient selection. We studied 14 symptomatic patients with hypertrophic cardiomyopathy, ages 20 to 61 years (mean 47),...
undergoing diagnostic right and left heart catheterization at the National Heart, Lung and Blood Institute. There were seven men and seven women. The diagnosis of hypertrophic cardiomyopathy was based in each patient on M mode and two-dimensional echocardiographic demonstration of a hypertrophied, nondilated left ventricle in the absence of another cardiac or systemic disease.5-7 All patients had disproportionate thickening of the ventricular septum with respect to the posterior left ventricular free wall (septal-to-free wall ratio of 1.5 to 2.7, mean 2.0). Ventricular septal thickness ranged from 16 to 32 mm (mean 23). All patients were symptomatically limited (New York Heart Association functional classes III and IV) despite medical therapy. All cardiac medications were discontinued before catheterization. Propranolol was stopped at least 48 hr before catheterization, and verapamil at least 36 hr before catheterization. Informed consent was obtained before catheterization.

**Hemodynamic measurements.** Right and left heart catheterization was performed by standard techniques for our laboratory. Left ventricular pressures were measured by fluid-filled pigtail catheters (end hole only, no side holes) in four patients and micromanometer transducer-tipped catheters (Millar Instruments, Inc., Houston) in 10 patients. Catheter entrapment was excluded by the guidelines proposed by Wigle et al.9 Cardiac output was measured with the right heart catheter by the thermodilution technique (thrombolytic cardiac output computer; Edwards Laboratories, Inc., Santa Ana, CA); for each cardiac output determination, the average of three measurements was computed. Left ventricular stroke volume was calculated from the cardiac output. Systemic blood pressure was monitored by means of a brachial artery catheter. Left ventricular end-systolic pressure was estimated by the dicrotic notch of the simultaneously recorded brachial artery pressure.

In the 10 patients studied with micromanometer catheters, left ventricular relaxation was assessed by computing the time constant (T) of left ventricular pressure fall after peak negative dP/dt.11 The logarithm of left ventricular pressure was plotted as a function of time every 5 msec for a total of 80 msec beginning at peak negative dP/dt. T was calculated as the inverse of the slope of the exponential equation describing this relationship. In several patients, a single exponential function did not adequately describe the change in pressure with time; in these patients, biexponential fitting was used, with one time constant (T1) describing the first 40 msec after peak negative dP/dt and another (T2) describing the next 40 msec.12 Peak negative dP/dt was not used as an index of left ventricular relaxation because of the significant decrease in peak left ventricular pressure after verapamil.11

Contrast left ventriculography was performed in the right anterior oblique projection to assess the presence and severity of mitral regurgitation. In six patients left ventriculography was performed during a previous catheterization, and in the other eight patients ventriculography was performed at the completion of the radionuclide measurements. In five patients there was no mitral regurgitation. In the other nine patients, mild mitral regurgitation (1+ to 2+) was present.

**Radionuclide measurements.** During placement of the right heart catheter, red blood cells were labeled in vivo with 15 to 20 mCi technetium-99m.13 Ten minutes after administration of technetium-99m, the patient underwent anticoagulation with heparin (5000 U, iv), and retrograde left heart catheterization was begun. After equilibration of the tracer in the blood pool, and after placement of catheters in the pulmonary artery and left ventricle, the scintillation probe was positioned over the left ventricle.

**Nonimaging scintillation probe.** The microprocessor-based scintillation probe system developed at the National Institutes of Health consists of a 7.5 cm diameter, 2.59 cm thick NaI crystal equipped with a high-sensitivity parallel-hole collimator permitting counting rates in excess of 40,000/sec.14 The nonimaging detector is interfaced to a microprocessor, which acquires, analyzes, and displays the scintillation data in real time. The linearity between counting rates and volume for the probe with parallel-hole collimation has been reported previously.14 Although changes in left ventricular counts in an individual patient are proportional to changes in left ventricular volume, the proportionality constant is unknown and varies from patient to patient. This precludes measurement of absolute volume changes and comparison among patients but allows comparison of relative changes occurring in each individual patient.

The angular position of the probe is fixed at an angle of 35 degrees left anterior oblique with a 15 degree caudal modification (similar to the modified left anterior oblique position adapted in our laboratory for routine Anger camera studies). At this fixed angle, the probe is adjusted over the precordium until a position is reached at which the background-uncorrected ejection fraction is maximum. This positioning scheme yields time-activity curves that show excellent agreement in shape and timing with curves derived from Anger camera studies; background-uncorrected ejection fractions also correlate excellently between probe and camera studies.14 The position of the probe was marked on the chest wall to facilitate repositioning. To determine background activity, the probe was masked with a 1 inch field of view and moved slowly from its position over the left ventricle toward the patient’s feet until the time-activity curve became flat. Although the uncertainty of the probe in quantitating absolute background activity may limit its usefulness in determining absolute left ventricular function, it is suited ideally for monitoring changes in left ventricular volume and function during short-term studies.14-16

Previous studies in our laboratory indicated that errors caused by background uncertainty with the probe can be minimized by using the ejection fraction determined by an Anger camera study to calculate the background offset of the probe study.14 Since the background region is visualized during a camera study but not during a probe study, potential errors in background determinations with the probe (such as those caused by increased splenic uptake) are reduced by determining background activity directly with a camera study. Hence, for this investigation a routine Anger camera study was performed at the completion of the catheterization laboratory study without a second radioisotope injection. The ejection fraction was then computed from the camera study by our standard technique17 and used to correct the probe data. This can be accomplished since both probe and camera are equipped with parallel-hole collimators.

ECG-gated equilibrium scintillation data were acquired by the probe for 140 cardiac cycles in LIST mode,14 from which high-temporal resolution time-activity curves of 25 msec/point were generated (figure 1). Cardiac cycles falling outside a set range of cardiac cycle lengths were excluded from analysis to minimize the effects of extrasystolic and postextrasystolic cycles. Combined forward and reverse gating from the R wave was used to reconstruct late diastolic volume changes.14,18 Stroke counts, which is background independent, was measured directly from the time-activity curve. End-diastolic counts, end-systolic counts, and ejection fraction were computed after background correction. In addition, left ventricular diastolic filling was assessed by fitting a third-color polynomial function to the rapid filling phase of the time-activity curve.5,18 The peak filling rate was taken as the maximum slope of the polynomial function, normalized for the number of counts at end-diastole, and expressed as end-diastolic volume (EDV) per second. Time to peak filling rate was measured from end-systole (nadir of the time-activity curve) to the time of peak left ventricular filling rate.

In 12 of 14 patients (including eight of nine patients with mitral regurgitation), changes in radionuclide stroke counts...
after verapamil were compared with changes in thermodilution stroke volume for validation. Changes in end-diastolic and end-systolic counts after verapamil were expressed as a percent of control counts to indicate changes in relative left ventricular volumes. These measurements were made not to compare the magnitude of difference among patients, but rather to compare directional changes occurring in each patient relative to his or her control values. Changes in left ventricular counts and background counts with time were corrected for physical decay of the isotope. In nine patients background activity was measured under control conditions and also at the completion of the study after verapamil infusions.

**Left ventricular pressure-volume analysis.** Analysis of left ventricular diastolic pressure-volume relations was performed in the 10 patients whose pressure measurements were obtained with micromanometer transducer-tipped catheters. In these patients the left ventricular pressure measurements represented another physiologic input signal to the microprocessor in addition to ECG input and counting data from the nonimaging detector. Like the time-activity curve, the left ventricular pressure curve was constructed by LIST mode ECG gating and was corrected for fluctuations in cycle length, with exclusion of extrasystolic and postextrasystolic cardiac cycles. From these primary data, instantaneous relations between left ventricular pressure and volume were analyzed via the automatic generation of high-temporal resolution pressure-count loops, representing the average of 140 cardiac cycles (figure 2).

**Drug administration.** After control pressure and volume measurements were obtained, verapamil was infused through a peripheral vein in three doses: 0.007, 0.014, and 0.021 mg/kg/min for 10 min each. For infusion was preceded by a 0.1 mg/kg bolus administered over a 2 min period. Repeat hemodynamic and radionuclide measurements were obtained at the completion of each 10 min infusion, whereupon the next increment in drug dosage was begun, preceded by a repeat bolus administration. Verapamil infusions were discontinued if the patient manifested atrioventricular block or decreases in arterial systolic pressure greater than 25 mm Hg compared with the control value, or if systolic pressure decreased below 85 mm Hg.

Complete hemodynamic and radionuclide data at all three doses of verapamil were obtained in three patients. In a fourth patient, radionuclide data collection during low- and medium-dose verapamil infusions were incomplete, but all data were obtained during high-dose (V3) verapamil infusion in this patient. Of the remaining 10 patients, only one complete dose of verapamil was administered to three patients and two doses to seven patients. In these patients, the next highest verapamil infusion was either not begun or was discontinued before measurements were made because of second-degree atrioventricular block (one patient), decrease in systolic blood pressure greater than 25 mm Hg compared with the control blood pressure (four patients), decrease in systolic arterial pressure below 85 mm Hg (four patients), or increase in pulmonary wedge pressure above 30 mm Hg (one patient).

**Variability of radionuclide measurements.** During the course of the catheterization studies, it was occasionally necessary to move and then reposition the probe over the left ventricle (e.g., to perform background measurements). To ensure that reproducible measurements could be achieved by the probe after repositioning, we performed probe studies in 10 other patients undergoing routine Anger camera studies in the Nuclear Cardiology Laboratory. The diagnosis in these patients were coronary artery disease (four patients), hypertrophic cardiomyopathy (two patients), aortic stenosis (two patients), aortic regurgitation (one patient), and restrictive cardiomyopathy (one patient). These patients underwent probe repositioning studies in which 10 consecutive probe measurements were made. During the first measurement, the position of the probe over the left ventricle was marked on the patient's chest. Between each measurement the probe was moved away from the chest and then repositioned over the left ventricle. End-diastolic counts, end-systolic counts, stroke counts, and ejection fraction were computed for each of the 10 studies per patient. Background was measured in each patient after the first and after the tenth left ventricular measurements. Changes in left ventricular counts and background counts with time were corrected for physical decay of the isotope.

**Statistical methods.** The effects of verapamil on left ventricular hemodynamics and radionuclide measurements were analyzed by the paired t test, comparing control and the highest dose of verapamil achieved for each patient. A repeat analysis was made comparing control and low-dose (V1) verapamil.

**Results**

**Control measurements.** Hemodynamic data obtained during control conditions for the 14 patients are shown in table 1. Ten patients manifested subvalvular left ventricular outflow tract gradients at rest ranging from 25 to 95 mm Hg. Four patients manifested no outflow tract gradient at rest or during provocation with Valsalva maneuver, amyl nitrite inhalation, or isoproterenol infusion. Left ventricular end-diastolic pressure ranged from 8 to 32 mm Hg and pulmonary capillary wedge pressure from 6 to 25 mm Hg. Supranormal left ventricular ejection fractions (≥72%) were observed in 13 patients. The ejection fraction was 68% in one patient. Thermodilution cardiac output ranged from 2.4 to 6.8 l/min, yielding left ventricular stroke volumes of 38 to 74 ml. Cardiac index ranged from 1.1 to

**FIGURE 1.** Time-activity curve derived from the scintillation probe as a measure of relative left ventricular (LV) volume changes during the average cardiac cycle. Stroke counts, which is background independent, is computed directly. Left ventricular end-diastolic counts (EDC) and end-systolic counts (ESC) are computed after background correction.
The increases in radionuclide stroke counts (mean 2.3 ± 0.7 [± SD]) and stroke volume index ranged from 19 to 41 ml/m² (mean 31 ± 7). Only four patients had a cardiac index greater than 2.5 l/min/m², the lower limit of normal.

**Effects of verapamil**

*Effects on left ventricular volume.* Relative changes in radionuclide stroke counts that occurred after verapamil administration were validated by the thermodilution technique in 12 of the 14 patients for a total of 21 verapamil doses. A good correlation (r = .87, SEE = 5.5) was observed between relative changes measured by the two techniques (figure 3). An excellent agreement was observed regarding relative directional changes (increases vs decreases).

During verapamil infusion, radionuclide end-diastolic and end-systolic counts significantly increased while background activity was unchanged, suggesting increased left ventricular volumes (table 1). These changes were dose related in most patients (figure 4). The increases in left ventricular diastolic and systolic counts were associated with decreases in left ventricular ejection fraction and increases in stroke counts (table 1, figure 4).

*Effects on left ventricular systolic pressure.* Arterial blood pressure significantly decreased during verapamil treatment (table 1). Despite this reduction in systemic pressure (which by itself would be expected to increase the outflow gradient), verapamil reduced the left ventricular outflow tract gradient in eight of the 10 patients with basal outflow gradients (table 1, figure 5); the pressure gradient decreased by 15 mm Hg or greater in eight patients and by 30 mm Hg or greater in five patients. This was associated with a significant decrease in left ventricular peak systolic pressure.

In 11 patients, the left ventricular end-systolic pressure-volume relation (with the dicrotic notch as a measure of end-systolic pressure) was shifted downward and rightward by verapamil (figures 2 and 6), suggesting a decrease in contractile function. In the other three patients, the change in end-systolic pressure and volume was horizontal, with higher end-systolic volume at unchanged end-systolic pressure. In all 14 patients the systolic pressure-volume relation was shifted downward and rightward when peak left ventricular pressure was used.

*Effects on left ventricular diastolic function.* The increases in end-systolic counts after verapamil were associated

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**FIGURE 2.** Simultaneous ECG-gated volume (counts) and pressure curves, from which instantaneous left ventricular (LV) pressure-volume relations may be analyzed from high-temporal resolution pressure-count loops. Each point represents 25 msec.
TABLE 1

Effect of verapamil on left ventricular hemodynamics

<table>
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<th>Patient no.</th>
<th>Highest verapamil dose</th>
<th>Heart rate (beats/min)</th>
<th>Arterial systolic BP (mm Hg)</th>
<th>ED counts ($\times 10^5$)</th>
<th>ES counts ($\times 10^5$)</th>
<th>Stroke counts ($\times 10^5$)</th>
<th>Ejection fraction (%)</th>
<th>PFR (EDV/sec)</th>
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<td>C V</td>
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<td>130 115</td>
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<td>1.69 1.87 (111)</td>
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<td>4.7 4.2</td>
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<td>125 130</td>
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<td>95 100</td>
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<td>125 115</td>
<td>6.89 8.67 (126)</td>
<td>1.94 2.55 (131)</td>
<td>4.95 6.12 (124)</td>
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<td>110 115</td>
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<td>0.36 0.81 (227)</td>
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<td>90 85</td>
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BP = blood pressure; C = control; EDV = end-diastolic volume (counts); LV = left ventricular; PCW = pulmonary capillary wedge; PFR = peak filling rate; V = verapamil (highest dose); ED = end-diastolic; ES = end-systolic.

$^A$Change expressed as percent of control counts.

$^A$Patients 11 through 14 had no left ventricular outflow gradient before or after verapamil; their data are not included in the mean outflow gradient calculations.

with no significant change in either left ventricular end-diastolic pressure or mean pulmonary capillary wedge pressure (table 1), although two patients had substantial increases in both left ventricular end-diastolic and pulmonary wedge pressure. The peak rate of left ventricular rapid diastolic filling, expressed relative to left ventricular end-diastolic counts, was not significantly changed by verapamil (table 1); peak filling rate increased in nine patients but decreased in five patients. Time to peak left ventricular filling rate significantly decreased after verapamil (control 207 ± 36 msec, verapamil 176 ± 40 msec; $p < .005$), with 11 patients showing a decrease.

Among the 10 patients in whom instantaneous left ventricular pressure-volume (counts) data were obtained, the diastolic pressure-volume curve was shifted downward and rightward by verapamil in five patients, reflecting improved pressure-volume relations (figure 7). In this subgroup, peak left ventricular filling rate, normalized for end-diastolic volume, increased after verapamil in all five (3.7 ± 1.0 EDV/sec control, 4.6 ± 0.6 EDV/sec verapamil; $p < .01$) and the time constant of relaxation decreased in all five (table 2), reflecting enhanced relaxation. In the other five patients the diastolic pressure-volume relation was not altered by verapamil (figure 8), and increased left ventricular diastolic volume occurred at higher end-diastolic pressures. The time constant of relaxation increased after verapamil in these patients (table 2), and peak filling rate decreased in four patients in this subgroup; in the fifth (patient 5), peak filling rate increased in association with substantial increases in both left ventricular end-diastolic pressure and mean pulmonary capillary wedge pressure (table 1). The effect of verapamil on the diastolic pressure-volume relation was not directly related to the highest dose of verapamil received by each patient (table 2) or to the magnitude of the changes in left ventricular volumes or peak systolic pressure.

Effects of low-dose verapamil. Since the two highest doses of verapamil used in this study potentially may result in plasma verapamil levels higher than those achieved during oral therapy, a repeat analysis of radionuclide and hemodynamic measurements was made comparing control and low-dose verapamil (table 3). This analysis also permitted comparison of the effect of
a single dose of verapamil in 13 of the 14 patients. As implied by the dose-related changes of left ventricular counts and pressures to verapamil (figures 4 and 5), the changes after low-dose verapamil were less marked than after highest-dose verapamil. Nonetheless, low-dose verapamil infusion produced significant increases in left ventricular end-diastolic counts, end-systolic counts, and stroke counts and significant reductions in left ventricular ejection fraction, peak systolic pressure, and outflow tract gradient. The end-systolic pressure-volume relation was shifted downward and rightward in 10 of the 13 patients. Left ventricular end-diastolic pressure and mean pulmonary capillary wedge pressure were unaltered by low-dose verapamil.

In six of the patients in whom instantaneous pressure-volume data were obtained, pressure-volume loops could be constructed at more than one verapamil dose. The directional changes in the pressure-volume relation induced by low-dose verapamil were identical to those observed at higher verapamil doses, although the magnitude of these changes was dose related.

**Variance of radionuclide measurements.** In the 10 patients studied with 10 serial measurements after probe repositioning, none of the radionuclide variables changed significantly after correction for physical decay of the isotope; background activity was also unchanged. To compare the reproducibility of these measurements between individual patients, the mean and standard deviation of the 10 studies in each patient were computed (table 4). The relative standard deviation (coefficient of variance) for end-diastolic counts, end-systolic counts, and stroke counts was then calculated by dividing the standard deviation by the mean, and these relative standard deviations were compared directly for the 10 patients. The mean standard deviation in end-diastolic counts for the 10 patients was 3.9%, the mean standard deviation in end-systolic counts was 8.2%, and the mean standard deviation in stroke counts was 9.1%. The standard deviation in ejection fraction was $3.1 \pm 1.8$ ejection fraction units.

In comparison, in the 14 hypertrophic cardiomyopathy patients, the percent change after verapamil (table 1) was $19 \pm 9\%$ (range 1% to 36%) for end-diastolic counts and $91 \pm 54\%$ (range 8% to 195%) for end-systolic counts. The increases after verapamil were greater than the expected variability of the probe measurements in 13 patients for end-diastolic counts and in 12 patients for end-systolic counts. The changes in stroke counts ($7 \pm 10\%$, range $-7\%$ to $+24\%$), despite a statistically significant increase, were within the error of the technique in all but two patients. However, similar changes in relative stroke volume by the thermodilution technique (figure 3) suggest that the directional changes (if not the absolute magnitude of these changes) in radionuclide stroke counts after verapamil are valid. The changes in left ventricular ejec-

### TABLE 1 (Continued)

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<th>Peak systolic pressure (mm Hg)</th>
<th>ED pressure (mm Hg)</th>
<th>Mean PCW pressure (mm Hg)</th>
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</tr>
<tr>
<td>40 39</td>
<td>8 7</td>
<td>7 8</td>
<td>27 35</td>
</tr>
</tbody>
</table>

$<.001$ NS NS $.01$

**FIGURE 3.** Relative changes in left ventricular (LV) stroke counts and thermodilution stroke volume after verapamil administration in 12 patients for a total of 21 verapamil doses. Percent change in radionuclide stroke counts for each verapamil dose relative to control is plotted as a function of the percent change in stroke volume by the thermodilution technique. Open circles, patients without LV outflow gradients.
FIGURE 4. Effects of verapamil on left ventricular (LV) end-diastolic counts, end-systolic counts, stroke counts, and ejection fraction. Data are shown for control (C) and for low- (V1), medium- (V2), and high-dose (V3) verapamil infusion. Changes in counts are expressed relative to control to indicate relative changes in LV volumes for each patient. Slashed circles indicate mean values. The mean values shown for verapamil in each panel represent the mean value at the highest verapamil dose achieved for each patient. Open circles, data obtained in four patients without LV outflow gradients.

Discussion

Nonimaging scintillation probe. In this study we investigated left ventricular pressure-volume relations with a nonimaging scintillation probe before and after intravenous verapamil administration. Because the methodologic uncertainties in determining absolute background activity with the nonimaging detector\textsuperscript{14} prevent the measurement of absolute changes in left ventricular volumes, and because the presence of mitral regurgitation in some patients may result in systematic underestimation of forward left ventricular stroke volume by our technique, the radionuclide data are presented as directional changes in relative left ventricular volumes and stroke volume rather than absolute volume changes. The reproducibility data and the good correlation between relative changes in thermodilution stroke volume and relative changes in radionuclide stroke counts (figure 3) indicate that the

FIGURE 5. Effects of verapamil on left ventricular outflow tract gradient under resting conditions in 10 patients. Symbols and abbreviations are explained in legend to figure 4.

FIGURE 6. Change in left ventricular (LV) end-systolic pressure from control to after verapamil relative to change in LV end-systolic counts. Circles indicate 10 patients with outflow tract gradients before verapamil, and triangles indicate four patients with no outflow gradients. Changes in end-systolic counts are expressed relative to control and are shown to indicate directional changes occurring in individual patients, not to compare the magnitude of change among patients.
relative changes in left ventricular volume and function after verapamil are valid. Previous studies of other probe systems indicate the validity of serial monitoring of left ventricular volume and function with time. The probe reproducibility studies in our laboratory indicate no inherent change in background activity with time. Although apparent increases in left ventricular counts (and reduction in apparent ejection fraction) might occur on the basis of increased background activity after acute verapamil administration, such increases were not observed. We have also observed no increases in background activity during Anger camera studies of oral verapamil therapy in over 50 patients with hypertrophic cardiomyopathy.

Effect of verapamil in hypertrophic cardiomyopathy. The left ventricle of patients with hypertrophic cardiomyopathy is characterized by myocardial hypertrophy,

TABLE 2
Effect of verapamil on left ventricular diastolic function

<table>
<thead>
<tr>
<th>Patient verapamil</th>
<th>Time constant of relaxation (msec)</th>
<th>PFR (EDV/sec)</th>
<th>Verapamil effect on pressure-volume relation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. A</td>
<td>T C V</td>
<td>T1 C V</td>
<td>T2 C V</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 V3</td>
<td>44 56</td>
<td>45 54</td>
<td>48 61</td>
</tr>
<tr>
<td>2 V3</td>
<td>61 81</td>
<td>94 148</td>
<td>34 43</td>
</tr>
<tr>
<td>5 V3</td>
<td>— —</td>
<td>54 84</td>
<td>69 86</td>
</tr>
<tr>
<td>12 V1</td>
<td>— —</td>
<td>79 86</td>
<td>110 117</td>
</tr>
<tr>
<td>7 V1</td>
<td>65 68</td>
<td>72 71</td>
<td>60 64</td>
</tr>
</tbody>
</table>

See table 1 for abbreviations.

*In three patients the total time constant could not be determined because of inadequate fitting of the time course of left ventricular pressure fall with a single exponential function.
impaired relaxation and filling, normal or reduced end-diastolic volume, and hyperdynamic contractile function.\textsuperscript{1, 3, 24-28} In patients with subvalvular outflow tract gradients, the pressure gradient is dynamic and responsive to changes in left ventricular volume and contractility.\textsuperscript{25, 27, 29} Previous studies have demonstrated that intravenous verapamil reduces the outflow tract gradient, even in patients in whom verapamil produces a marked decrease in systemic blood pressure.\textsuperscript{5} One objective of the current study was to investigate the mechanisms for this effect.

The 14 patients included in this study had features typical of hypertrophic cardiomyopathy. Ten had subvalvular pressure gradients of 25 mm Hg or greater, and 13 manifested hypercontractile left ventricles with ejection fractions of 72\% or greater. Despite the increased ejection fraction, both stroke volume and cardiac index were subnormal in 10 patients.

Verapamil administration produced significant negative inotropic effects on left ventricular systolic function, with reduced ejection fraction, increased end-diastolic and end-systolic counts (from which we infer increased left ventricular volumes), and decreased end-systolic pressure. The end-systolic pressure-volume relation was shifted consistently downward and rightward, suggesting decreased contractile function.\textsuperscript{20} These changes were associated with significant reductions in left ventricular outflow gradient in those patients with gradients. Although these changes were dose related and most marked at higher verapamil doses (figures 4 and 5), significant alterations were also evident during low-dose verapamil infusion (table 3). These findings are in contrast with previous data indicating no effect of intravenous verapamil on left ventricular systolic function.\textsuperscript{1, 3, 30}

Intravenous verapamil did not improve left ventricular diastolic function in all patients. However, enhanced diastolic function was observed in a subgroup of patients after verapamil. In these patients verapamil reduced the time constant of relaxation, increased the peak rate of rapid diastolic filling, and shifted the diastolic pressure-volume relation downward and rightward toward higher volume at lower pressure (figure 8).

![Graphs showing time-activity curves before and after verapamil](image)

**FIGURE 8.** Time-activity curves before and after verapamil (left). The peak rate of left ventricular (LV) rapid diastolic filling, expressed relative to end-diastolic volume, was unchanged by verapamil. The diastolic pressure-volume relation (right) was not altered by verapamil.

<p>| TABLE 3 |
| Effects of low-dose verapamil\textsuperscript{a} |</p>
<table>
<thead>
<tr>
<th>Control</th>
<th>Verapamil (V\textsubscript{s})</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>75 ± 13</td>
<td>75 ± 12</td>
</tr>
<tr>
<td>Arterial systolic pressure (mm Hg)</td>
<td>115 ± 15</td>
<td>111 ± 17</td>
</tr>
<tr>
<td>Radionuclide data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED counts (% of control)</td>
<td>100</td>
<td>113 ± 11</td>
</tr>
<tr>
<td>ES counts (% of control)</td>
<td>100</td>
<td>152 ± 49</td>
</tr>
<tr>
<td>Stroke counts (% of control)</td>
<td>100</td>
<td>107 ± 9</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>83 ± 8</td>
<td>79 ± 9</td>
</tr>
<tr>
<td>PFR (EDV/sec)</td>
<td>3.9 ± 1.4</td>
<td>4.1 ± 1.2</td>
</tr>
<tr>
<td>Time to PFR (msec)</td>
<td>208 ± 37</td>
<td>190 ± 45</td>
</tr>
<tr>
<td>LV pressure data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak systolic pressure (mm Hg)</td>
<td>159 ± 42</td>
<td>142 ± 40</td>
</tr>
<tr>
<td>ED pressure (mm Hg)</td>
<td>18 ± 8</td>
<td>18 ± 7</td>
</tr>
<tr>
<td>Mean PCW pressure (mm Hg)</td>
<td>16 ± 7</td>
<td>17 ± 8</td>
</tr>
<tr>
<td>Outflow gradient (mm Hg)\textsuperscript{b}</td>
<td>61 ± 44</td>
<td>28 ± 33</td>
</tr>
</tbody>
</table>

See table 1 for abbreviations.

\textsuperscript{a}Data (mean ± SD) are shown for 13 of the 14 patients. One patient (No. 3) did not have adequate radionuclide data during low-dose verapamil infusion.

\textsuperscript{b}Outflow gradient data are shown for the nine patients with resting outflow gradients before verapamil.
7). We cannot determine from our data whether these effects represent a primary effect of verapamil on left ventricular relaxation and filling or whether they occur secondary to changes in left ventricular loading conditions. However, this improvement in left ventricular relaxation and filling after intravenous verapamil was observed despite the negative inotropic effect, which would by itself be expected to diminish indexes of left ventricular relaxation and diastolic function.\textsuperscript{31-34} Intra-
venous verapamil was found to cause similar improve-
ment in diastolic relaxation and filling in the echocar-
diographic study of Hanrath et al.\textsuperscript{3}

In a second subgroup of patients in our study, however, improved diastolic function could not be documented. In these five patients the diastolic pressure-volume curve was not altered by verapamil and increased diastolic volumes occurred at higher diastolic pressures (figure 8). The time constant of relaxation increased in these five patients, and the peak rate of ventricular filling (normalized for end-diastolic vol-
ume) decreased in four. In one patient an increased rate of diastolic filling developed in the setting of alarming increases in left ventricular end-diastolic pressure and pulmonary capillary wedge pressure. Presumably, an elevated left atrial pressure, with resulting increased driving pressures across the mitral valve, served to increase the rate of rapid ventricular filling in this patient.\textsuperscript{32}

It cannot be ascertained from our study whether verapamil actually had no salutary effect on diastolic function in this second subgroup of five patients or whether such an effect was present but was masked by other actions of the drug. For example, the negative inotropic action of verapamil could diminish the rate of diastolic filling,\textsuperscript{32, 34} shift the diastolic pressure-volume relation toward increased end-diastolic pressure,\textsuperscript{33} and increase the time constant of left ventricular relax-
ation.\textsuperscript{33} Moreover, since the time constant of relaxation depends on left ventricular loading conditions,\textsuperscript{32, 33, 35} the rate of left ventricular relaxation may also be mod-
ulated by verapamil-induced changes in end-diastolic and end-systolic volumes and end-systolic pressure.

The increase in left ventricular stroke volume after intravenous verapamil in our study and that of Hanrath et al.\textsuperscript{3} suggests, at first glance, that contractile function of the left ventricle was not diminished by verapamil. Our data, however, are more compatible with the concept that the hemodynamic changes we observed were caused by two concurrent but opposing actions of the drug. That verapamil did decrease contractile function is evidenced by the reduced ejection fraction and the rightward and downward shift of the end-systolic pressure-volume relation. One mechanism responsible for the increase in stroke volume, despite a decrease in contractile function, could derive from verapamil effects on left ventricular relaxation and filling, producing increased end-diastolic volumes. Hence, increased left ventricular stroke volume in some patients after verapamil could result from the primary increase in end-diastolic volume via a Frank-Starling mechanism. Additional mechanisms that could have contributed in some patients to the increased stroke volume, despite a decrease in contractile function, derive from the drug-
induced reduction in obstruction to left ventricular out-
flow and arterial pressure; both of these effects would lead to a decrease in impedance to left ventricular

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\begin{table}
\centering
\caption{THERAPY AND PREVENTION--HYPERTROPHIC CARDIOMYOPATHY}
\begin{tabular}{lccccccccccc}
\hline
\textbf{Patient} & \textbf{Diagnosis} & \textbf{End-diastolic counts} & \textbf{End-systolic counts} & \textbf{Stroke counts} & \textbf{Ejection fraction} \\
No. & & Mean & SD & SD(%) & Mean & SD & SD(%) & Mean & SD & SD(%) \\
\hline
1 & HCM & 13,696 & 395 & 2.8 & 2,386 & 245 & 10.3 & 11,291 & 237 & 2.4 & 82.6 & 1.4 \\
2 & AS & 19,807 & 253 & 1.2 & 9,997 & 1,433 & 14.3 & 9,810 & 1,514 & 15.4 & 49.5 & 7.4 \\
3 & RCM & 18,026 & 843 & 4.6 & 12,330 & 406 & 3.3 & 5,696 & 518 & 10.2 & 31.5 & 2.1 \\
4 & CAD & 18,035 & 669 & 3.7 & 13,272 & 913 & 6.9 & 4,763 & 551 & 11.6 & 26.4 & 3.3 \\
5 & CAD & 13,181 & 466 & 3.5 & 8,406 & 721 & 8.5 & 4,775 & 627 & 13.1 & 36.2 & 4.8 \\
6 & CAD & 15,519 & 819 & 5.3 & 11,322 & 898 & 7.9 & 4,141 & 528 & 12.7 & 27.1 & 3.3 \\
7 & AR & 14,666 & 373 & 2.5 & 3,919 & 300 & 7.7 & 10,747 & 487 & 4.5 & 73.3 & 2.2 \\
8 & CAD & 14,214 & 570 & 4.0 & 11,040 & 354 & 3.2 & 3,174 & 345 & 10.9 & 22.3 & 1.8 \\
9 & AS & 17,548 & 727 & 4.1 & 9,381 & 498 & 5.3 & 8,167 & 390 & 4.8 & 46.6 & 1.5 \\
10 & HCM & 13,362 & 917 & 6.9 & 4,231 & 621 & 14.7 & 9,130 & 460 & 5.0 & 68.4 & 2.8 \\
\hline
\textbf{Mean} & 3.9 & & & 8.2 & & & 9.1 & & & 3.1 & & \\
\end{tabular}
\end{table}

AR = aortic regurgitation; AS = aortic stenosis; CAD = coronary artery disease; HCM = hypertrophic cardiomyopathy; RCM = restrictive cardiomyopathy.

\textsuperscript{a}Data are based on 10 studies in each patient after background correction.

\textsuperscript{b}Relative SD = (SD/mean) \times 100.
ejection. The effect of such changes on cardiac output and stroke volume might attenuate the opposing actions caused by a verapamil-induced decrease in contractile state.

Extrapolation of the results of this short-term intravenous study to long-term oral verapamil therapy is difficult because it is uncertain which of the intravenous verapamil infusion rates achieves tissue verapamil levels comparable to those achieved by oral administration. The two highest intravenous verapamil doses often result in plasma verapamil levels that are higher than those achieved by oral administration. However, during long-term oral verapamil treatment in patients with hypertrophic cardiomyopathy, changes in left ventricular volumes similar to those in the current study have been demonstrated, with increases in end-diastolic volume and stroke volume associated with a reduction in outflow tract gradient. Oral verapamil in doses of 360 to 480 mg/day also increases the peak rate of left ventricular rapid diastolic filling, both short-term and long-term, as assessed by radionuclide angiocardiographic Anger camera studies. Unlike the results of the current study, however, these short- and long-term studies of oral therapy failed to demonstrate significant verapamil-induced reduction in left ventricular ejection fraction. Despite no significant change in mean ejection fraction, we have observed decreases in ejection fraction in individual patients during oral therapy that are comparable to the effects of low-dose intravenous verapamil in the present study. In a series of 55 patients, nine (16%) had a decrease in ejection fraction of 5% or greater during oral verapamil, 320 to 480 mg/day. In addition, in six of 10 patients studied by Kaltenbach et al., long-term oral verapamil therapy resulted in both reduced outflow gradient and increased left ventricular end-systolic volume. Hence, although the effects on left ventricular volumes and diastolic filling appear to predominate during oral verapamil therapy, changes compatible with a negative inotropic effect may be observed in some patients.

These data suggest that several interrelated effects on left ventricular systolic and diastolic function in patients with hypertrophic cardiomyopathy may be clinically relevant. For example, the improved diastolic pressure-volume relations resulting from improved left ventricular relaxation and filling, the direct negative inotropic actions, and the complex interaction between these effects lead, in many instances, to an increase in stroke volume and cardiac output without significant increases in pulmonary venous pressures, as well as to a reduction in outflow gradient. Each of these changes may contribute to the salutary clinical results observed in many individual patients during verapamil therapy.

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Effects of verapamil on left ventricular systolic and diastolic function in patients with hypertrophic cardiomyopathy: pressure-volume analysis with a nonimaging scintillation probe.

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