Left Ventricular End-Diastolic Pressure-Volume Relationships in Hypertrophic Cardiomyopathy* 

Changes Induced by Verapamil

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In 16 patients with hypertrophic cardiomyopathy, an acute response of the left ventricular end-diastolic pressure and volume index to intravenously administered verapamil was assessed. Verapamil decreased the left ventricular end-diastolic pressure from 20 ± 6 to 17 ± 5 mm Hg (p<0.001) and increased the end-diastolic volume index from 82 ± 22 to 91 ± 23 ml/m² (p<0.01). In 13 (81 percent) of 16 patients, an improvement of end-diastolic pressure-volume relationships occurred. In hypertrophic cardiomyopathy, intravenous verapamil exerts a beneficial effect on left ventricular filling conditions, producing an augmentation of filling volume at a lower filling pressure.

Verapamil has been found to be a promising drug in the treatment of hypertrophic cardiomyopathy. Both symptomatic improvement* and beneficial hemodynamic effects6,7,10,11 were reported. Results of some studies indicate that verapamil may actually reverse hypertrophy in patients with hypertrophic cardiomyopathy;4,5,12 however, this opinion has not gained wide acceptance.7

The present study was undertaken to evaluate changes in left ventricular end-diastolic pressure and volume in the setting of acute administration of verapamil and to determine if these changes depend on the baseline hemodynamic measurements.

Materials and Methods

Sixteen patients (3 men and three women) aged 17 to 51 years (mean ± SD, 33 ± 10 years) were studied. All had echocardiographic evidence of asymmetric septal hypertrophy with a septal to free wall thickness ratio greater than 1.5.3,4 in the absence of other cardiac disease. All patients were in sinus rhythm. An intraventricular pressure gradient of 20 to 130 mm Hg (mean, 49.9 ± 36.7 mm Hg) was found in eight patients; in the remaining eight, no gradient was demonstrated. All medications were withheld for 48 hours prior to the investigation. The nature of the procedure was explained to each patient, and informed consent was obtained.

After premedication with 10 mg of diazepam orally, a Swan-Ganz thermodilution catheter was placed in the pulmonary artery. Left heart catheterization was performed using a pigtail catheter (Cordis F 8). Pressures were measured by means of transducers (Statham P 23 1D), with the zero reference point at midchest level. Left ventricular end-diastolic pressure (LVEDP) was measured 50 msec after the onset of the QRS complex. Cardiac output was calculated by a cardiac output computer (Edwards Laboratories 9520 A).

After obtaining baseline pressures and cardiac output, a single-plane left ventriculographic study in the 30° right anterior oblique projection was performed. Only technically adequate ventriculograms, without catheter-induced arrhythmias, were analyzed. Twenty minutes after the first ventriculogram, measurements of cardiac output and pressure were repeated. In all patients, these values were found to have returned to baseline. At that point an intravenous injection of verapamil (Isoptin) was given in a dosage of 0.1 mg/kg of body weight over two minutes, followed by infusion of 0.01 mg/kg/min. After ten minutes of the infusion, all measurements of pressure, as well as left ventriculograms, were done again.

Left ventricular volumes were calculated according to the area-length method,6 the left ventricular mass index was established by the method of Backley et al.,6 and the mean thickness of left ventricular free wall was measured with a planimeter. Selective coronary arteriograms employing the Judkins technique completed the study in all patients. No obstructive coronary lesions were found.

In order to assess the influence of systolic loading conditions on diastolic measurements, peak systolic pressures in the aorta and left ventricle, as well as basal left ventricular outflow gradients, were also measured. Data were analyzed statistically using Student’s t-test.

Results

The results are summarized in Table 1. Verapamil significantly decreased both left ventricular peak systolic pressure from 136 ± 41 to 115 ± 30 mm Hg (p<0.001) and systolic aortic pressure from 111 ± 17 to 102 ± 15 mm Hg (p<0.001). The left ventricular outflow gradient, present at rest in eight patients, was reduced by verapamil in seven and remained unchanged in one (baseline gradient, 50 ± 37 mm Hg; gradient after verapamil, 25 ± 28 mm Hg [p<0.001]). In no instance did the gradient increase, even though the fall in peak aortic pressure was a uniform concomitant finding.

The LVEDP declined by 1 to 8 mm Hg in 14 patients, remained unchanged in one, and rose by 3 mm Hg in one patient. The mean value for LVEDP dropped from 20 ± 6 to 17 ± 5 mm Hg (p<0.001). This represents an average decrease in LVEDP by 3 mm Hg (15 percent of the control value).

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Manuscript received November 29, revision accepted February 24.
Table 1—Baseline Hemodynamic Data and Verapamil-Induced Changes in Patients with Hypertrophic Cardiomyopathy*

<table>
<thead>
<tr>
<th>Case</th>
<th>LVEDP (mm Hg)</th>
<th>LVEDVI (ml sq m)</th>
<th>LVESVI (ml sq m)</th>
<th>Heart Rate, beats per min</th>
<th>LVSP (mm Hg)</th>
<th>AoSP (mm Hg)</th>
<th>Basal LV Outflow Gradient (mm Hg)</th>
<th>LV Mass Index, g sq m</th>
<th>LV Free Wall Thickness, mm</th>
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<td>75§</td>
<td>78§</td>
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* B, Baseline; A, after verapamil; LV, left ventricular; LVSP, left ventricular peak systolic pressure; and AoSP, aortic peak systolic pressure.
†p<0.001 for B vs A.
‡p<0.01 for B vs A.
§p<0.02 for B vs A.

The left ventricular end-diastolic volume index (LVEDVI) increased after verapamil from the mean value of $82 \pm 22$ to $91 \pm 23$ ml sq m (p<0.01). The mean rise in LVEDVI was 9 ml sq m (11 percent of the control value). The LVEDVI remained virtually unchanged (in a range of $\pm 3$ ml sq m) in five subjects, rose in ten, and declined by 12 ml sq m in one subject.

The left ventricular end-systolic volume index (LVESVI) was not uniformly changed. The LVESVI remained unchanged in nine patients, rose in five, and decreased in two. The difference between mean values of $18 \pm 7$ ml sq m in the control state and $19 \pm 7$ ml sq m after verapamil was not statistically significant.

Figure 1 shows changes in end-diastolic pressure-volume relationships induced by verapamil. In 12 patients (six with and six without obstruction), the relationships shifted downwards and to the right; in one (with a low basal gradient), the LVEDVI rose while LVEDP remained unchanged. This group of 13 patients (81 percent) represents a fraction in whom verapamil favorably modified left ventricular filling conditions.

Of the remaining three patients, two showed a decrease in both pressure and volume, and in one, end-diastolic pressure increased with no change in volume. This last patient had no basal outflow obstruction.

Relationships between changes in LVEDVI and LVEDP vs baseline hemodynamic indices are shown in Table 2. Changes in LVEDVI did not depend on the

Table 2—Correlation Coefficients between Verapamil-Induced Changes and Baseline Hemodynamic Values*

<table>
<thead>
<tr>
<th>x</th>
<th>$\Delta$LVEDV†</th>
<th>$\Delta$LVEDP†</th>
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<tbody>
<tr>
<td>LVEDVI</td>
<td>$r = -0.167$</td>
<td>$r = 0.226$</td>
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<tr>
<td>LVEDP</td>
<td>$r = 0.159$</td>
<td>$r = -0.528$</td>
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<td>LV mass index</td>
<td>$r = 0.204$</td>
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<tr>
<td>LV free wall thickness</td>
<td>$r = 0.347$</td>
<td>$r = -0.132$</td>
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*LV, Left ventricular.
†Changes induced by verapamil.
‡p<0.05.
baseline values. A significant negative correlation was found between the extent of verapamil-induced changes in LVEDP and baseline LVEDP ($r = -0.528$; $p < 0.05$; Fig 2).

There was no significant correlation between changes in peak left ventricular systolic pressure induced by verapamil and changes in LVEDP ($r = -0.117$) and LVEDVI ($r = 0.311$).

**DISCUSSION**

The present study demonstrates that intravenous infusion of verapamil in patients with hypertrophic cardiomyopathy in most instances lowers LVEDP and increases LVEDVI. This indicates a beneficial effect on end-diastolic pressure-volume relations, with larger filling volumes occurring at lower pressure.

All patients included in this study had elevated LVEDP. Verapamil decreased this pressure significantly, both in patients with and without obstruction. In normal subjects and in patients with conditions other than hypertrophic cardiomyopathy, verapamil tends to elevate LVEDP due to its negative inotropic effect. In our group of patients, we observed a substantial decrease in LVEDP, congruent with the former observations by Kaltenbach et al., Bonow et al., and Rosing et al. Only one patient, with the non-obstructive form of the disease, had an elevation of the LVEDP (13 to 16 mm Hg). Elevation of LVEDP after verapamil in patients with normal or near normal baseline values appears to be a common form of response.

Left ventricular volumes were calculated from two consecutive ventriculograms. Values after verapamil may have been affected by the first injection of contrast material; however, hemodynamic changes induced by the contrast medium should be negligible 15 to 20 minutes after injection. We virtually excluded this effect by starting administration of verapamil after cardiac output and left ventricular pressures had returned to baseline. Bonow et al., using radionuclide techniques, recently reported increasing LVEDV with higher doses of verapamil in patients with hypertrophic cardiomyopathy, further supporting the view that this finding results from direct action of verapamil, and not of the contrast material.

The most pronounced pathophysiologic feature of hypertrophic cardiomyopathy is an impairment of diastolic compliance. The verapamil-induced shift of left ventricular end-diastolic pressure-volume relations represents improved filling. Whether this effect is due to a true change in compliance is not clear, since the diastolic pressure-volume curve can be affected not only by changes in passive mechanical properties of the myocardium, but also by changes in relaxation, systolic loading conditions, and interaction between the two ventricles.

As pointed out by Glantz and Parmley, it may be difficult to sort out, even with high-fidelity measurements, what mechanisms are involved. Therefore, it was not an objective of this study to clarify the mechanism, but rather to see if verapamil can beneficially modify the altered end-diastolic pressure-volume relations.

In 13 (81 percent) of 16 patients studied, verapamil acutely improved LVEDP and LVEDVI or improved the LVEDP without affecting the volume.

Epstein and Rosing state that patients with the obstructive form of the disease may adversely respond to verapamil. We did not see any detrimental hemodynamic effect with intravenous verapamil in any of our patients. The left ventricular outflow gradient declined in all eight patients in whom it was present in baseline conditions. In none of them was a rise in LVEDP observed.

The extent of improvement in LVEDVI and LVEDV was not related to the baseline ventricular diastolic volume, nor to left ventricular mass index, wall thickness, or change in systolic loading conditions. Thus, none of those measurements can serve as a predictor of the efficacy of verapamil in a particular patient. In our study the drop in LVEDP induced by verapamil tended to be greater in patients with higher left ventricular filling pressures. Although the correlation was significant, it was weak and with considerable individual variations, so that the response of a given patient to verapamil could not be established from baseline hemodynamic measurements.

Whether an acute response to the drug carries any information regarding predictability of the results in long-term treatment remains questionable.

We conclude that in a considerable percentage of patients with hypertrophic cardiomyopathy, intravenous verapamil acutely improves left ventricular end-diastolic pressure-volume relationships, resulting...

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**Figure 2.** Correlation between changes in LVEDP produced by verapamil and baseline values.
in lowered filling pressure and an augmented filling volume. Response to verapamil cannot be predicted on the grounds of baseline hemodynamic findings and has to be assessed in every patient individually.

ACKNOWLEDGMENT: We thank Dr. W. B. Campbell for review of the manuscript.

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