Verapamil Therapy: A New Approach to the Pharmacologic Treatment of Hypertrophic Cardiomyopathy

I. Hemodynamic Effects

SUMMARY The hemodynamic effects of intravenous verapamil administration were examined in 27 patients with hypertrophic cardiomyopathy. Increasing doses of verapamil produced small increases in heart rate and cardiac output and a significant decrease in systolic blood pressure, but had no significant effect on mean pulmonary artery wedge pressure or left ventricular end-diastolic pressure. The highest dose of verapamil increased heart rate from 72 ± 3 to 81 ± 6 beats/min and reduced systolic blood pressure from 118 ± 8 to 99 ± 5 mm Hg (p < 0.005). This dose decreased the basal left ventricular outflow tract gradient from 94 ± 14 to 49 ± 14 mm Hg and the average left ventricular outflow tract gradient during the Valsalva maneuver from 76 ± 5 to 63 ± 13 mm Hg, during amyl nitrite inhalation from 69 ± 15 to 39 ± 13 mm Hg, and during isoproterenol infusion from 108 ± 29 to 70 ± 21 mm Hg (p < 0.01). These results indicate that verapamil can significantly decrease left ventricular outflow obstruction in patients with hypertrophic cardiomyopathy and thus may provide an important new therapeutic agent in the treatment of this disorder.

FOR MANY YEARS propranolol has been the primary pharmacologic therapeutic agent for symptomatic patients with hypertrophic cardiomyopathy.\(^1\)\(^-\)\(^3\) The salutary hemodynamic and symptomatic effects produced by propranolol derive from its inhibition of sympathetic stimulation to the heart.\(^4\)\(^-\)\(^5\) However, there is no evidence that the drug alters the primary cardiomyopathic process; many patients remain in or return to their severely symptomatic states, and some die, despite its administration.\(^2\)\(^,\)\(^3\)

If propranolol therapy fails to control symptoms in patients with obstruction to left ventricular outflow, an operation such as septal myotomy-myectomy must be considered. Although this operation provides marked symptomatic benefit to most patients with obstruction to left ventricular outflow, the operative risks are 5–10%.\(^6\)\(^,\)\(^7\) Moreover, operation is not a viable option for patients without obstruction. Therefore, new approaches to the nonoperative treatment of this disease are clearly necessary.

One of the striking characteristics of the left ventricle in hypertrophic cardiomyopathy is its hypercontractile state, manifest by end-systolic apical cavity obliteration and increased ejection fraction. One hypothesis for this hypercontractility suggests that there are increased amounts of norepinephrine in the left ventricle of patients with hypertrophic cardiomyopathy.\(^8\) However, this hypothesis has never been confirmed and there is no explanation for the hypercontractile state in this disorder.

Because increases in myocardial cell calcium content increase myocardial contractility,\(^8\) we were intrigued by the studies of the hereditary cardiomyopathy of Syrian hamsters.\(^10\)\(^-\)\(^12\) These studies showed that myocardial calcium uptake and content are increased and that the metabolic and anatomic abnormalities can be prevented by the administration of verapamil, an agent that blocks inward calcium transport across cell membranes.

There is no evidence that the cardiomyopathy of the Syrian hamster is the same disease as hypertrophic
cardiomyopathy in man. However, the finding of a hyperdynamic left ventricle in hypertrophic cardiomyopathy in man raises the possibility that myocardial calcium overload might, as in the Syrian hamster, account for some of the cardiac abnormalities leading to symptoms and death. A report by Kaltenbach and associates, indicating that the administration of verapamil to patients with hypertrophic cardiomyopathy reduces symptoms, and the anecdotal report by Goodwin, proposing that drugs like verapamil, which inhibit inward calcium transport through the so-called slow channel, might be beneficial in patients with hypertrophic cardiomyopathy, suggested that this hypothesis merited further exploration. We therefore examined the hemodynamic effects of verapamil in a group of patients with hypertrophic cardiomyopathy.

Methods

Subjects

Twenty-seven patients, 16 men and 11 women, ages 21–68 years (mean ± SEM 44 ± 3 years), had echocardiographic evidence of asymmetric septal hypertrophy (septal-to-posterobasal left ventricular free wall thickness ratio ≥1.3) in the absence of other types of acquired or congenital heart disease. All agreed to participate in the study according to a protocol approved by the Clinical Research Subpanel of the National Heart, Lung, and Blood Institute. The criterion for the obstructive form of hypertrophic cardiomyopathy was the presence of at least 30 mm Hg subaortic peak systolic pressure gradient in the basal state or during provocation with the Valsalva maneuver, amyl nitrite inhalation or intravenous isoproterenol infusion. The criteria for the non-obstructive form of hypertrophic cardiomyopathy was the absence of such a gradient. Twenty-six patients fulfilled the criterion for obstructive hypertrophic cardiomyopathy. The one patient without obstruction at the time of study had had a previous septal myotomy.

Twenty-one patients underwent hemodynamic study because of clinically important dyspnea, angina, presyncope or syncope, despite an adequate trial of propranolol. Propranolol had been administered in doses 80–480 mg/day (median 320 mg/day). Two other patients had the same severe symptoms, but could not tolerate propranolol. The remaining four patients were in a stable condition and underwent catheterization for diagnostic purposes only. Cardiac medications were discontinued at least 5 drug half-lives before catheterization. Each patient received intramuscular pentobarbital 1 hour before study and took nothing by mouth for at least 8 hours before study. Each patient gave informed consent for all procedures.

Hemodynamic Measurements

Left ventricular pressure was obtained through a pigtail catheter (end-hole only, no side holes) placed in the apex of the left ventricle by the retrograde femoral technique. Catheter entrapment was excluded by the guidelines proposed by Wigle et al. Pulmonary artery wedge pressure was obtained through a Courmand catheter placed by the antegrade femoral technique. Cardiac output was determined from indocyanine green dye-dilution curves.

All patients were in normal sinus rhythm when hemodynamic measurements were made. Measurements were initially recorded in the control state and then 10–20 minutes after each dose of verapamil. In all patients who had basal left ventricular outflow tract gradients <70 mm Hg and in an occasional patient with a gradient of 70–90 mm Hg, the Valsalva maneuver, amyl nitrite inhalation and intravenous isoproterenol infusion were performed after basal measurements were obtained. When possible, left ventricular outflow gradients obtained before and during verapamil infusion were compared at similar heart rates (±10 beats/min) and systolic blood pressures (±15 mm Hg). Although verapamil administration sometimes lowered systemic systolic blood pressure by more than 15 mm Hg (vs control pressure), systolic pressure was never more than 15 mm Hg above that of the control state.

Verapamil Infusions

Verapamil was infused into a peripheral vein in three dosages: 0.007, 0.014 and 0.021 mg/kg/min. Each infusion was preceded by a 0.1-mg/kg bolus of verapamil administered over 2 minutes. In the first 10 patients studied, only 0.007 mg/kg/min was used and hemodynamic measurements were made at 10 and 20 minutes. When multiple dosages were administered, measurements were made after 10 minutes of infusion, whereupon the next increment in drug dosage was begun, preceded by a repeat bolus administration.

Statistics

Data were analyzed statistically using the two-tailed r test for paired data.

Results

Basal Hemodynamics

The two higher verapamil dosages produced a small increase in heart rate, while systolic blood pressure decreased significantly at all three dosage levels (table 1, figs. 1 and 2). Mean pulmonary artery wedge pressure for the overall group did not change significantly with increasing verapamil dosages (table 1 and fig. 3). However, in five of seven patients, a high control wedge pressure fell by 4–12 mm Hg. Only four of 19 patients with normal control wedge pressure developed an abnormal mean pulmonary artery wedge pressure (>15 mm Hg) during verapamil infusion (fig. 3). Left ventricular end-diastolic pressure for the group did not change significantly (table 1 and fig. 4). However, left ventricular end-diastolic pressure fell (10 patients) or was unchanged (two patients) in 12 of the 15 patients who had abnormal pressures in the
control state. The decrease in pressure ranged from 1-14 mm Hg (fig. 4). Five of 10 patients with normal control end-diastolic pressures developed abnormal pressures (>12 mm Hg) during verapamil infusion. Cardiac index was maintained during verapamil infusion and increased significantly at the highest dose of verapamil when there was a mild rise from a control value of 2.5 ± 0.2 to 2.8 ± 0.2 l/min/m² (p < 0.05) (table 1 and fig. 5).

In the 14 patients with a basal left ventricular outflow tract gradient ≥30 mm Hg, the mean basal gradient decreased with increasing verapamil infusions (table 2 and fig. 6). Three patients had their basal gradients reduced to <30 mm Hg by the drug infusions. The only patient whose gradient increased markedly with verapamil administration (35 to 80 mm Hg) had a simultaneous fall in systolic blood pressure from 160 to 105 mm Hg.

**Provocable Gradients**

In the control state, 12 of 15 patients who performed a Valsalva maneuver developed a left ventricular outflow tract gradient ≥30 mm Hg. In eight of these 12 patients, a 25% or greater decrease in the Valsalva-induced gradient occurred during the verapamil infusion (table 2 and fig. 7). Two of the four nonresponders had a markedly lower systolic blood pressure.

### Table 1. Hemodynamic Effects of Verapamil

<table>
<thead>
<tr>
<th>No. of pts</th>
<th>Control</th>
<th>Verapamil infusion (mg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>27</td>
<td>76 ± 3</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>27</td>
<td>116 ± 4</td>
</tr>
<tr>
<td>Mean pulmonary artery wedge pressure (mm Hg)</td>
<td>25</td>
<td>14 ± 1</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>25</td>
<td>16 ± 2</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>24</td>
<td>2.6 ± 0.1</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

*p < 0.05 vs control.

†p < 0.01 vs control.

‡p < 0.005 vs control.

§p < 0.001 vs control.

### Table 2. Effect of Verapamil on Left Ventricular Outflow Tract Gradients (mm Hg)

<table>
<thead>
<tr>
<th>Gradient</th>
<th>No. of pts</th>
<th>Control</th>
<th>Verapamil infusion (mg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>Basal</td>
<td>14</td>
<td>86 ± 7</td>
<td>64 ± 8*</td>
</tr>
<tr>
<td>Valsalva-induced</td>
<td>12</td>
<td>90 ± 8</td>
<td>74 ± 9</td>
</tr>
<tr>
<td>Amyl nitrite-induced</td>
<td>10</td>
<td>80 ± 10</td>
<td>56 ± 11†</td>
</tr>
<tr>
<td>Isoproterenol-induced</td>
<td>9</td>
<td>107 ± 15</td>
<td>79 ± 14‡</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

*p < 0.05 vs control.

†p < 0.01 vs control.

‡p < 0.005 vs control.
Control 0.007 0.014 0.021
VERAPAMIL INFUSION, mg/kg/min

FIGURE 1. Effect of increasing doses of verapamil on heart rate. Horizontal bars indicate mean values.

Control 0.007 0.014 0.021
VERAPAMIL INFUSION, mg/kg/min

FIGURE 2. Effect of increasing doses of verapamil on systolic blood pressure. Horizontal bars indicate mean values.

FIGURE 3. Effect of increasing doses of verapamil on mean pulmonary artery wedge pressure. Horizontal bars indicate mean values. Broken line indicates upper limit of normal pressure. Asterisk indicates direct left atrial measurements obtained when the catheter crossed a patent foramen ovale.

pressure with the Valsalva maneuver during verapamil infusion (fig. 7).

Amyl nitrite inhalation produced a gradient of ≥30 mm Hg in the control situation in 11 of 12 patients to whom it was administered. Verapamil reduced the gradient induced by amyl nitrite >25% in nine of these 11 patients (table 2 and fig. 7). Both patients in whom verapamil had no effect on the gradient induced by amyl nitrite had a systolic blood pressure >30 mm Hg lower than in the control state at the time of the peak gradient measurement (fig. 7). One of these patients received only the lowest dose of verapamil.

All 10 patients who received an isoproterenol infusion developed a gradient ≥30 mm Hg in the control state. Verapamil decreased the isoproterenol-induced gradient at least 25% in all 10 patients (table 2 and fig. 7).

Adverse Effects

In two patients, systolic blood pressure decreased to less than 90 mm Hg and for this reason they did not receive the highest dose of verapamil. PR prolongation occurred in all patients; the longest PR interval attained was 380 msec (from a control of 200 msec). The mean PR interval in the control state was 177 ± 6 msec and increased to 199 ± 6 msec (p < 0.001), 218 ± 10 msec (p < 0.001), and 244 ± 17 msec...
VERAPAMIL IN HYPERTROPHIC CARDIOMYOPATHY I/Rosing et al.

Figure 4. Effect of increasing doses of verapamil on left ventricular end-diastolic pressure. Horizontal bars indicate mean values. Broken line indicates upper limit of normal pressure. ($p < 0.005$) with increasing doses of verapamil. Two patients had occasional nonconducted sinus beats at the highest dose. No other abnormalities in cardiac conduction or adverse effects were noted.

Discussion

The present study shows that the intravenous administration of verapamil to patients with hypertrophic cardiomyopathy diminished basal and provoked left ventricular outflow tract gradients in a dose-related manner (table 2, figs. 6 and 7), while cardiac output either remained the same or increased slightly (table 1 and fig. 5). Cardiac output was maintained when the left ventricular outflow gradient was reduced, indicating that the fall in gradient resulted from an actual increase in the effective orifice size of the left ventricular outflow tract.

In addition to having no detrimental effect on cardiac output, verapamil administration produced no clinically important increase in mean pulmonary artery wedge or left ventricular end-diastolic pressures. Although left-sided filling pressures rose after verapamil in a number of patients, these increases occurred mainly in patients who had normal pressures in the control state, and in no patient did either pressure rise above 20 mm Hg. Wedge and end-diastolic pressures decreased or did not change in

Figure 5. Effect of increasing doses of verapamil on cardiac output. Horizontal bars indicate mean values.

Figure 6. Effect of increasing doses of verapamil on basal left ventricular outflow tract gradient. Broken line with open circles indicates a patient whose systolic blood pressure decreased by more than 15 mm Hg during verapamil administration. Horizontal bars indicate mean values.
most patients who began the study with abnormal left-sided filling pressures (figs. 3 and 4).

Despite these beneficial hemodynamic effects of verapamil, several considerations must be kept in mind. First, only 11 of our 27 patients received the highest (0.021 mg/kg/min) dose of verapamil used in this study, and clinically important increases in left-heart filling pressures might have been observed if more patients had received the higher doses. Second, reductions in systemic resistance, and thereby arterial pressure, may increase left ventricular outflow obstruction in patients with obstructive hypertrophic cardiomyopathy. Several patients in this study in whom systemic systolic blood pressure dropped >15 mm Hg had no decrease in left ventricular outflow tract gradient, and one patient actually had a marked increase in gradient. Hence, left ventricular outflow obstruction might be increased and the clinical situation worsened in a patient who responds to the drug with an appreciable decrease in systemic arterial pressure. Finally, we do not know what the relation is between the intravenous doses used in this study and the presently recommended oral doses of the drug. As with other drugs that have a high hepatic extraction from the portal blood before reaching the systemic circulation, there will probably be great individual variation in the hemodynamic effect of a given dosage. Thus, our results should not be construed as indicating that verapamil, when administered as a therapeutic agent, can usually be expected to be effective and totally safe. Patients receiving this medication must still be watched closely for signs of congestive heart failure as well as a depression of either the sinus node or conduction in the atrioventricular tissue. In addition, blood pressure must be frequently monitored in both the supine and upright positions to ensure that there is no tendency for an excessive decrease in peripheral vascular resistance.

The basic pharmacologic mechanisms by which verapamil exerts its diverse effects are presently unclear. Although earlier studies suggested verapamil had β-adrenergic receptor blocking activity, subsequent investigations have refuted this concept. More recently, verapamil has been shown to inhibit transmembrane fluxes of calcium. It appears that the drug specifically interferes with calcium transport occurring through the so-called slow channel. Although there is some evidence that verapamil blocks other ion fluxes through the slow channel, it is unclear whether such ionic transport actually occurs normally, or, if it does, what effect verapamil has on this transport.

Regardless of its precise biochemical effects, verapamil's major cardiovascular actions are to diminish the rate of conduction through atrioventricular tissue and to relax vascular smooth muscle, as well as other smooth muscle throughout the body. Potential adverse effects of the drug accrue from its ability to depress sinus node function, to produce atrioventricular block and to cause severe hypotension secondary to its vasodilatory activity. The drug has been shown to be capable of decreasing myocardial contractility in vitro at high concentration. Although depression in contractility also occurs experimentally in vivo and other studies have not confirmed this finding, these conflicting results may result from the different drug doses used, the different experimental models and the relative contributions of the direct and indirect actions of verapamil in the various studies.

The mechanisms responsible for the beneficial hemodynamic effects of verapamil in patients with hypertrophic cardiomyopathy probably derive, as do its adverse effects, from inhibition of calcium movement into the myocardial cell. Any agent that produces a decrease in the contractile state of the heart should, nonspecifically, diminish the degree of left ventricular outflow obstruction in patients with hypertrophic cardiomyopathy. This is believed to be the major mechanism by which propranolol reduces the outflow gradient in such patients. Thus, if verapamil decreases the myocardial contractile state by decreasing normal calcium transport or by correcting a basic abnormality involving excessive uptake of calcium by the myocardium, a decrease in outflow obstruction would be anticipated. Further studies will be necessary to determine which, if either, mechanism
applies to patients with hypertrophic cardiomyopathy.

Regardless of whether the beneficial hemodynamic effects exerted by verapamil are due to a nonspecific effect of the drug on myocardial contractile state or to reversal of the biochemical consequences of a basic metabolic abnormality, our results suggest that verapamil may provide a new alternative to propranolol and operation in the treatment of hypertrophic cardiomyopathy. Moreover, if results of further studies suggest a specific role of calcium antagonists in the treatment of hypertrophic cardiomyopathy, a much broader application of verapamil to the therapy of this disease may be indicated.

Acknowledgment

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