Chronic Verapamil Therapy in Pediatric and Young Adult Patients with Hypertrophic Cardiomyopathy

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Oral verapamil, 5.2 ± 1.1 mg/kg/day (range 2.8 to 7), was administered to 13 pediatric patients with hypertrophic cardiomyopathy for 13 ± 6 months (range 2 to 20). The patients had significant symptomatic improvement on verapamil therapy. Murmur intensity diminished in 6 patients during therapy and left ventricular (LV) electromotive forces on the electrocardiogram diminished in 4, increased in 5 and did not change in 4. Exercise endurance increased from 8.4 ± 3.9 to 10.9 ± 2.8 minutes (p <0.01). Seven patients had ST-segment depression (0.38 ± 0.28 mV) before verapamil therapy, which improved after verapamil therapy in 5 (0.24 ± 0.17 mV, p <0.02). Of 4 patients with exercise-induced ventricular ectopic activity, 3 had diminution or abolishment of ectopy following verapamil. By echocardiography, the patients had an increase in LV end-diastolic dimension from 3.4 ± 0.7 to 3.9 ± 0.8 cm (p <0.01), with no significant change in shortening fraction (46.1 ± 8.0% vs 44.6 ± 8.0%). When adjusted for body size and age there was a significant decrease in LV septal thickness (from 106 ± 70 to 45 ± 52% of predicted normal values, p <0.05) and LV posterior wall thickness (from 40 ± 45 to 5 ± 26% of predicted normal values p = 0.05) after verapamil. Isovolumic relaxation time decreased from 69 ± 26 to 42 ± 19 ms after verapamil (p <0.01). Systolic anterior motion of the anterior mitral leaflet disappeared in 5 of 8 patients and midsystolic closure of the aortic valve was no longer present in 4 of 8. Chronic oral verapamil appears to be an effective form of therapy for pediatric patients with hypertrophic cardiomyopathy. (Am J Cardiol 1984;53:1614–1619)

Intravenous verapamil administration has been shown to acutely improve the hemodynamic status of adults,[1,2] adolescents, and children[3] with hypertrophic cardiomyopathy (HC). Chronic oral verapamil therapy in adults has improved symptomatic status,[2,4,5] exercise capacity[4,5] and was associated with few side effects.[4-6] Verapamil has also been reported to improve left ventricular (LV) relaxation and filling,[3,7,8] and diminish ventricular septal thickness[9] and LV muscle mass.[2] We studied the effect of chronic oral verapamil therapy in a group of children, adolescents and young adults with HC.

Methods

Subjects: The study group consisted of 13 patients, aged 7 months to 19 years (mean 12 years), with echocardiographic findings of a nondilated, hypertrophic left ventricle. Intracardiac hemodynamics were measured in all 13 patients using percutaneous right and left retrograde femoral artery and right femoral vein catheterization (Table I). Simultaneous LV and thoracic aortic pressures were measured using a Millar micromanometer catheter and a UMI pigtail catheter, respectively. The acute hemodynamic effects of intravenous verapamil in 9 of these patients have been described.[3]

At cardiac catheterization, LV outflow obstruction at rest greater than 10 mm Hg was present in 8 of 13 patients. These 8 patients had a peak systolic ejection gradient of 30 to 139 mm Hg (mean 74) after provocation with isoproterenol, Valsalva maneuver, premature ventricular contractions or exercise testing as previously described. Five patients had a nonobstructive form of the disease, with rest and provokable systolic outflow tract gradients of less than 30 mm Hg.

Before institution of verapamil therapy, all 13 patients had dyspnea at rest or with exercise, 8 had angina pectoris at rest or with exercise, 8 had dizziness and near syncope and 2 had syncope. Symptoms persisted or increased despite propranolol therapy in 6 patients and septal myomectomy in 1 patient.

TABLE I   Patient Population

| Pt | Age (yr) & Sex | Obstructive (+) or Nonobstructive (−) (LVOT) | Symptoms | | | | Verapamil (mg/day) | Duration of Therapy (mos) |
			Dyspnea	Angina	Dizziness/ Postural Hypotension	Syncope		
1	0.6M	+ (45)	+	0	0	Cardiac arrest	28	14
2	4M	0	+	+	0	0	45	20
3	7M	+ (46)	+	+	0	0	160	14
4	8F	+ (30)	+	0	0	0	240	16
5	11M	+ (139)	+	0	0	0	240	12
6	12F	0	+	+	+	0	320	18
7	12M	+ (115)	+	+	+	0	240	3
8	15M	0	+	+	+	+	360	19
9	16M	+ (120)	+	0	+	0	360	4
10	17M	+ (35)	+	+	+	0	360	18
11	18F	0	+	+	+	0	320	14
12	18F	0	+	0	+	0	320	2
13	19M	+ (64)	+	+	+	+	360	13

LVOT = maximal left ventricular outflow tract gradient in mm Hg.

Each patient began oral verapamil therapy while hospitalized. Ten of 13 patients had oral verapamil started 24 hours after receiving intravenous verapamil at cardiac catheterization. Patient 9 (Table I) underwent catheterization at an outside institution 16 months before initiation of oral verapamil therapy. Patients 2 and 11 had sinus bradycardia with junctional escape rhythm after intravenous verapamil and did not receive oral verapamil initially. However, because of increasing symptoms, 1 of these patients received oral verapamil 1 month later and the other 2 months after catheterization.

Drug administration: Verapamil (40 or 80 mg capsule or as 2 mg/ml solution) was administered 3 or 4 times daily in doses of 2.8 to 7 mg/kg/day (mean 5.2). Dosage was selected to achieve plasma verapamil levels similar to those achieved at the time of intravenous verapamil administration.[3,10] Verapamil levels were measured at the first (2 to 4 months) and the second (4 to 6 months) clinic visit using gas chromatography with a nitrogen detector.[11]

Follow-up evaluation: All patients were evaluated with a complete history and physical examination initially at 2-month intervals and later, if doing well clinically, at 6-month intervals after initiation of verapamil therapy. Subjective assessment of any change in frequency, severity and duration of symptoms was made.

Standard 12-lead electrocardiograms (ECG) were performed before verapamil therapy and at each follow-up visit. Determination of the frontal-plane QRS axis, R-wave amplitude in standard lead aVL and the sum of the R wave lead V_5 and the S wave in V_1 were made. Tracings were also analyzed for ventricular ectopic activity and conduction abnormalities.

M-mode echocardiography was performed at rest in all patients before initiation of verapamil and at 2- to 6-month intervals after beginning therapy. All recordings were made using an Irex System 2 recorder, a 5.0- or 2.5-MHz transducer, and simultaneous ECG. LV dimension was recorded at a level inferior to mitral valve leaflet insertion while scanning the interventricular septum and LV posterior wall. End-diastolic dimension was measured at the onset of the QRS complex on the ECG, and systolic dimension at the peak of posterior LV wall motion. Shortening fraction of the left ventricle was determined by subtracting end-systolic diameter from end-diastolic diameter and dividing by end-diastolic diameter. Isovolumic relaxation (IVR) time was calculated according to the equation: (Q wave to aortic valve closure) − (Q wave to mitral valve opening [ms]). Measurements of ventricular septum and LV posterior wall were taken just inferior to the mitral valve leaflets at the onset of the QRS complex.

Ten patients performed graded treadmill exercise tests using the Bruce protocol[12] before and at 2- to 6-month intervals while receiving verapamil therapy. Patients exercised to exhaustion using a Quinton model 18-49-C treadmill with (model 644) program control and continuous strip-chart readout and oscilloscope ECG on an Electronics for Medicine VR-6. Modified leads II, aVF and V_5 were used to record the ECG. Heart rate and rhythm were measured directly from strip-chart electrocardiographic readout. Horizontal or negative ST-segment depression (relative to the PR baseline) was measured 80 ms after the J point.[13] Blood pressure was monitored at 3-minute intervals, at completion of exercise and during recovery using a Critikon stress monitor with chart recorder model 1165 and appropriate blood pressure cuff sizes. Exercise end points were exhaustion, lightheadedness, chest pain accompanied by ST-segment abnormalities and serious atrial or ventricular arrhythmia (i.e., supraventricular or ventricular tachycardia or heart block).

Statistical analysis: Data were analyzed and compared using the 2-tailed t test for paired data. Values are presented as mean ± standard deviation. Echocardiographic measurements of septal thickness, posterior wall thickness and diastolic dimension were normalized for age and body surface area and compared as a percentage of predicted value[14] using a paired t test.

Results

Follow-up: Duration of follow-up after initiation of oral verapamil therapy in the 13 patients was 2 to 19 months (mean 11). No patient has had verapamil therapy discontinued because of adverse effects or medication intolerance.

Physical examination and history: During the follow-up, all patients grew in size: The mean body surface area of the group increased from 1.32 ± 0.48 to 1.38 ± 0.46 m^2. Twelve patients had evidence of a systolic ejection murmur in the aortic region before institution of verapamil therapy. In 5 patients the murmur was grade 3/6[15] or greater. After verapamil therapy, murmur intensity decreased by 1 grade or more in 6 patients (5 of whom had obstructive disease) and remained unchanged in the other 6. Heart rate and systolic blood pressure at rest did not change significantly during verapamil therapy (Fig. 1).

An improved sense of well being was reported by the patient or the patient's parent (Fig. 2). Dyspnea, present

in all 13 patients before verapamil therapy, was absent in 7 patients and diminished in 6. These latter 6 patients reported an increase in exercise tolerance along with the decrease in frequency and severity of dyspnea.

Of the 8 patients with angina before verapamil, 5, followed for 14 to 19 months (mean 17.7), no longer had angina at rest or with activity. The other 3 patients, who have been treated for 5 to 13 months, have had notable decreases in frequency and severity of angina. Dizziness, lightheadedness or near syncope upon mild exertion or upon assuming upright posture was reported in 8 patients before verapamil therapy. After treatment with verapamil for 2 to 19 months (mean 11.7), only 1 of the 8 patients had dizziness, and this patient had it much less frequently. Syncope not associated with palpitations, angina or cardiac arrest was present in 2 of 13 patients before verapamil. After receiving verapamil for 19 and 13 months, respectively, 1 reported no syncopal episodes and 1 had a single episode.

Our first and youngest patient to receive verapamil (patient 1) had severe bronchopulmonary dysplasia in addition to HC.[3] This patient was weaned from mechanical ventilation and oxygen dependency and discharged home within 5 weeks of beginning verapamil treatment. The patient was treated with verapamil as an outpatient for 14 months when pneumonia developed and he died. At postmortem examination the ventricular septum was noted to be diffusely thickened without any localized subaortic or subpulmonic hypertrophy. Microscopic sections of the septum, right ventricular wall and LV wall showed distorted myocardium with interlacing bizarre bundles of myocardium containing hypertrophied muscle fibers and hypertrophied, hyperchromatic and elongated nuclei. Extensive fibrosis was noted between the individual muscle fibers and in large bands separating the muscle off into whorls and fascicles.

Electrocardiographic studies: Before verapamil therapy, a standard ECG disclosed normal sinus rhythm

in 11 patients, coronary sinus rhythm in 1 patient and atrial flutter in 1 patient. Patient 3 had Wolff-Parkinson-White syndrome and patient 7 had ventricular bigeminy. LV hypertrophy (defined as the sum of the R wave in V_5 and the S wave in V_1 greater than 35 mm or the R wave in aVL greater than 11 mm)[16,17] was noted in 5 patients. Right ventricular hypertrophy[17] was present in the 2 youngest patients. The mean QRS axis before verapamil therapy was 63 ± 58°.

After verapamil therapy, 12 of 13 patients had sinus rhythm; in 1 patient, atrial flutter persisted. The mean PR interval of the group was 140 ms before and after verapamil administration. The mean QRS axis after verapamil was unchanged, 65 ± 59°. The sum of S_{V_1} + R_{V_5} was greater in 5 patients, smaller in 4 patients and unchanged (±2 mm) in 4 after verapamil treatment. The R-wave amplitude in aVL was decreased in 3, increased in 3 and unchanged in 7 patients after verapamil therapy. Patients 2, 4, 6, 8, 9, 11 and 12 had either a decrease or no change in both S_{V_1} + R_{V_5} and RaV_L. In the 5 patients who met criteria for LV hypertrophy, 2 showed decreased and 2 increased LV voltages with treatment. The mean sum of S_{V_1} + Rv_5 in this group, however, showed no significant change after verapamil (62 ± 20 vs 62 ± 25 mm).

Exercise testing: Graded treadmill exercise testing was performed without complications in 10 patients who had received verapamil for 2 to 19 months (mean 11.3). Patients 1 and 2 did not undergo exercise testing because of size and patient 11 did not undergo exercise testing because of orthopedic deformities. Mean exercise endurance before verapamil was 8.4 ± 3.9 minutes (range 45 seconds to 14.5 minutes) and increased during verapamil therapy in all 10 patients to 10.9 ± 2.8 minutes (p <0.01) (Fig. 3). In 7 of the patients 0.1 mV of ST-segment depression developed in 1 or more leads during exercise testing (Fig. 3). After verapamil treatment, ST-segment depression with exercise improved
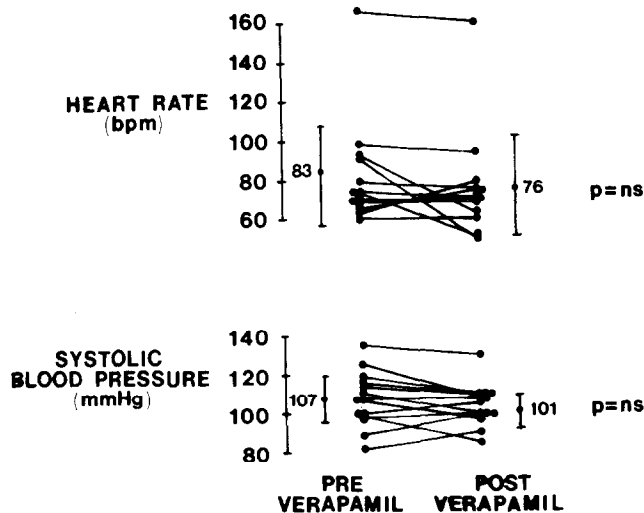

FIGURE 1. Effect of verapamil on heart rate and systolic blood pressure at rest. Values are mean ± standard deviation. ns = not significant.
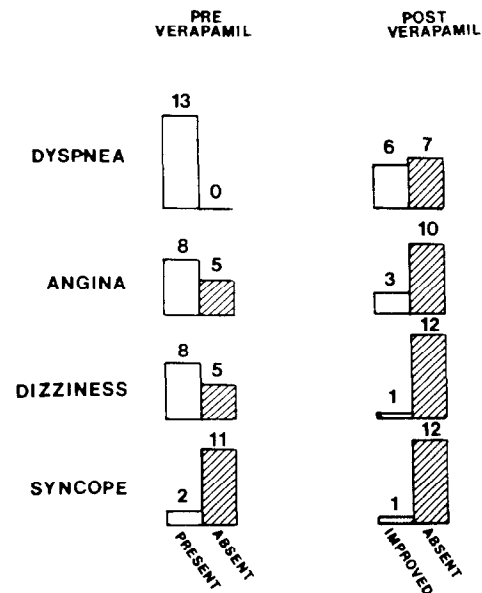

FIGURE 2. Symptoms before and after verapamil therapy in the 13 patients.

in 5 of 7 patients and was abolished in 2. Mean ST-segment depression decreased from 0.38 ± 0.28 to 0.24 ± 0.17 mV (p <0.02) (Fig. 3). There was no significant change in the maximal exercise rate-pressure product. The rate-pressure product was 21,715 before and 21,536 mm Hg/min after verapamil therapy (Fig. 3).

Four patients had ventricular ectopic activity elicited during exercise testing before beginning verapamil therapy: Lown[18] grade 4A (8 couplets in patient 7 and 3 in patient 9), grade 2 (>2 premature ventricular beats/min) in patient 4 and grade 1 (<20 premature ventricular beats/hour) in patient 3. After verapamil treatment for a mean of 9.25 months (range 4 to 16), ectopy was no longer produced by exercise in patients 3 and 9, it improved in patient 4 to grade 1 (<30 premature ventricular beats/hour) and persisted unchanged in patient 7 (4 couplets and frequent multiformed premature ventricular beats).

M-mode echocardiographic studies: An increase in LV end-diastolic dimension from 3.4 ± 0.7 to 3.9 ± 0.8 cm (p <0.01) occurred after verapamil therapy. There was little change in shortening fraction (46.1 ± 8.0 vs 44.6 ± 8.0%) (Fig. 4). The absolute changes in mean interventricular septal thickness (1.6 ± 0.05 vs 1.2 ± 0.5 cm), LV posterior wall thickness (0.9 ± 0.4 to 0.8 ± 0.2 cm), and the ratio of septal thickness/posterior wall (1.8 ± 0.5 to 1.5 ± 0.4) were not statistically significant (Fig. 5). However, several patients had dramatic decreases in septal thickness while receiving verapamil treatment (Fig. 6). Because most of our patients were growing children or adolescents, the echocardiographic measurements had to be adjusted for growth in order to determine whether changes in these variables actually occurred. When septal thickness, posterior wall thickness and end-diastolic dimension were compared with predicted normal values for age and body surface

area[14] and expressed as percent of predicted, mean septal thickness decreased from 106 ± 70% to 45 ± 52% (p <0.05) and mean posterior wall thickness from 40 ± 45% to 5 ± 26% (p = 0.05), and end-diastolic dimension increased from −18.8 ± 10% to −8 ± 9.8% (p <0.02).

After therapy with verapamil, mean IVR time decreased from 68.8 ± 26.0 to 41.9 ± 19.2 ms (p <0.01). IVR time decreased in 10 patients, increased slightly in 2 and did not change in 1 patient (Fig. 7).

Systolic anterior motion of the mitral valve was noted in 8 patients (6 obstructive and 2 nonobstructive) before verapamil therapy. This echocardiographic finding disappeared in 5 of the 8 after verapamil therapy. Early systolic closure of the aortic valve was seen in 8 patients, 7 of whom had obstruction. After treatment, 4 of these patients had disappearance of early closure. Five patients, all with obstructive myopathy, had both systolic anterior motion and early systolic closure of the aortic valve. After treatment with verapamil patients 3, 5 and 7 had disappearance of both findings.

Discussion

Chronic oral verapamil therapy in this pediatric population with HC resulted in improvement in symptomatic status. Similar levels of improvement have been noted in adults.[2,4,5] Accompanying the improved symptomatic status was an increase in treadmill exercise test endurance, less exercise-induced ST-segment depression, and a diminution in ventricular ectopy during exercise. The increased exercise endurance is similar to that achieved after acute drug testing[3] and in adults receiving chronic verapamil therapy.[4,5] Although this improvement may relate in part to retesting, previous studies in children with no known cardiac disease showed no improvement in exercise endurance when tests were repeated 1 hour to 1 year (mean 3 months) apart.[19] The improvement may also be a result of "training" secondary to increased activity levels that developed as symptoms decreased. The dramatic improvement observed in the patient's ST changes at comparable heart rate and blood pressure response and
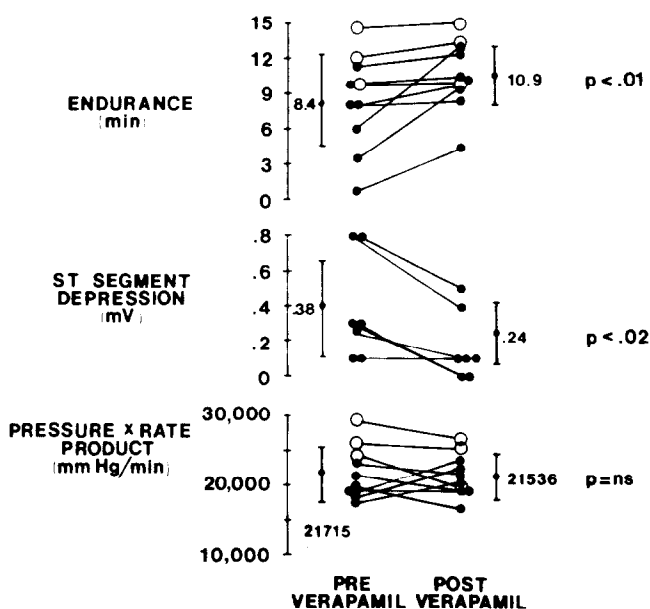
FIGURE 3. Effect of verapamil on exercise endurance, exercise-induced ST depression and rate-pressure product. Values are mean ± standard deviation. O = ST depression >0.1 mV; ● = no ST depression; ns = not significant.
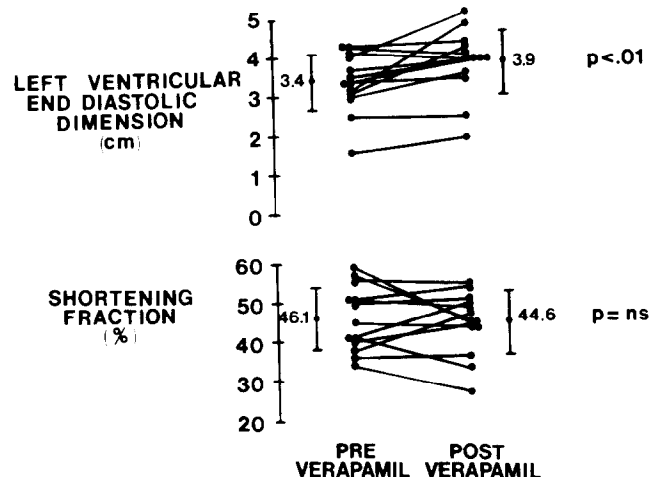
FIGURE 4. Effect of verapamil on echocardiographic measurement of end-diastolic dimension and shortening fraction. Values are mean ± standard deviation. ns = not significant.
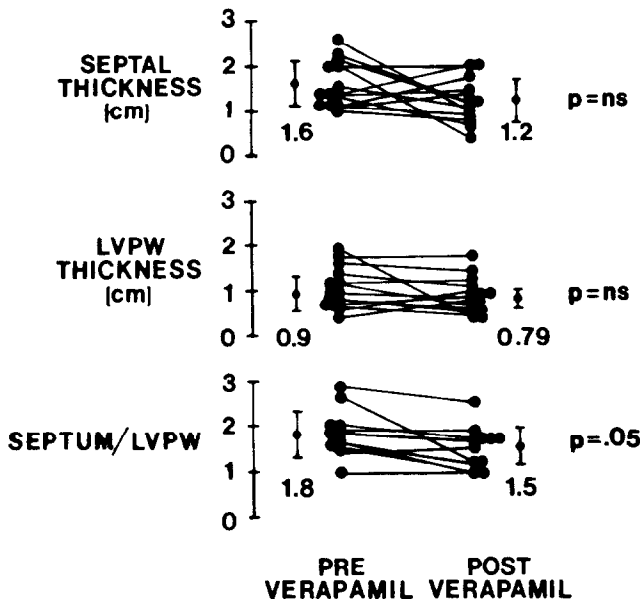
FIGURE 5. Effect of verapamil on echocardiographic measurement of septal thickness, left ventricular posterior wall (LVPW) thickness, and septum/LVPW ratio. Values are mean ± standard deviation. ns = not significant.

despite exercising longer than before verapamil therapy suggests that verapamil influenced the pathophysiologic process of the cardiomyopathy. Improved exercise capacity may be related to a diminution in LV outflow obstruction and decrease in LV end-diastolic pressure, known to occur with acute verapamil administration.[3] Likewise, angina, dyspnea, dizziness, and syncope, common complaints in pediatric patients with hyper-

trophic cardiomyopathy,[3,20] may be directly or indirectly related to elevated LV end-diastolic pressure or LV outflow obstruction. Chronic verapamil therapy, by improving these hemodynamic variables, may alleviate these symptoms.

The decrease in intensity of the systolic murmur in 6 of the patients also suggests a change in LV outflow dynamics with chronic verapamil therapy. Echocardiographic evaluation of these patients before verapamil revealed that either systolic anterior motion of the mitral valve or early systolic closure of the aortic valve—2 indicators of LV obstruction[21]—were present in all patients with obstructive disease and in 3 of 5 with nonobstructive disease. Only patients with obstruction, however, had both systolic anterior motion and early closure. The disappearance of systolic anterior motion and early closure in 50% of the patients after verapamil treatment suggests that outflow tract obstruction may be diminished by oral verapamil therapy. This is supported by our studies done with acute verapamil administration,[3] and may explain the diminution in murmur intensity noted in several of the patients.

How verapamil alters the LV outflow obstruction is not certain. However, we[3] and others[7,8,22] have postulated that improved diastolic relaxation and filling contributes to hemodynamic and clinical improvement. The significant decrease in IVR time demonstrated in this study may augment ventricular filling, which in turn results in increased end-diastolic volume, a finding also confirmed by the echocardiographic studies. The observed increase in end-diastolic dimension was much greater than the 1-mm increase expected with an increase in body surface area from 1.33 to 1.38 m^2.[23] This
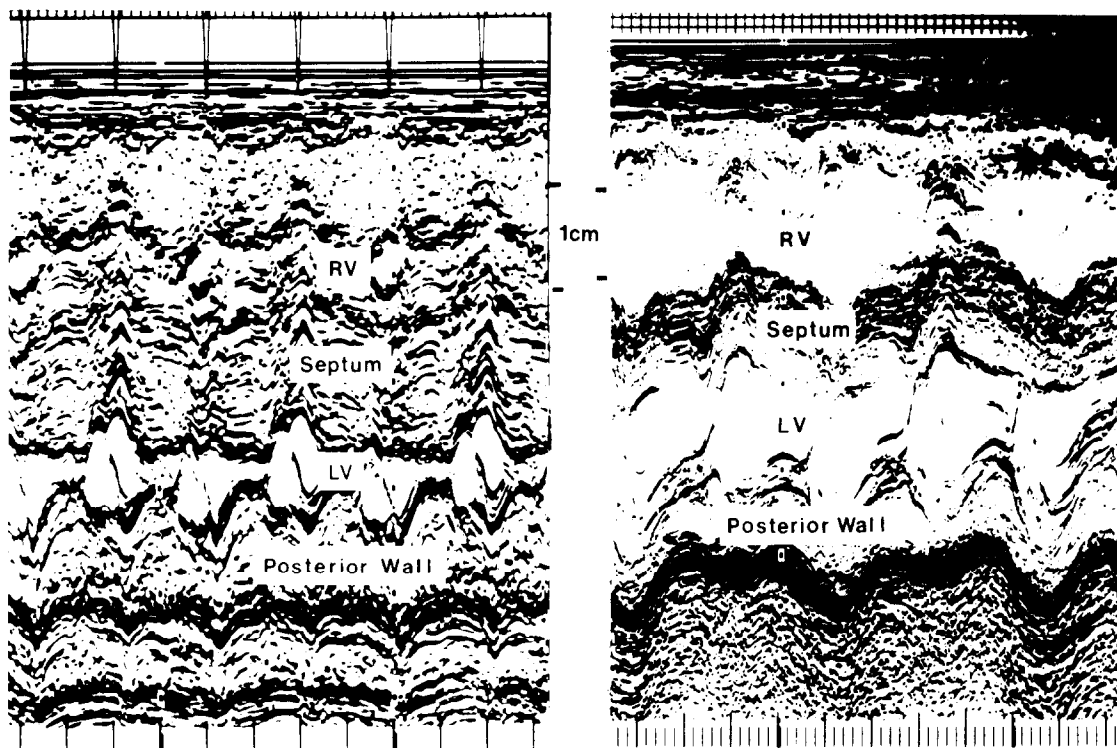

FIGURE 6. Echocardiographic changes in patient 1 before and after verapamil therapy for 1 year. RV = right ventricular cavity; LV = left ventricular cavity.
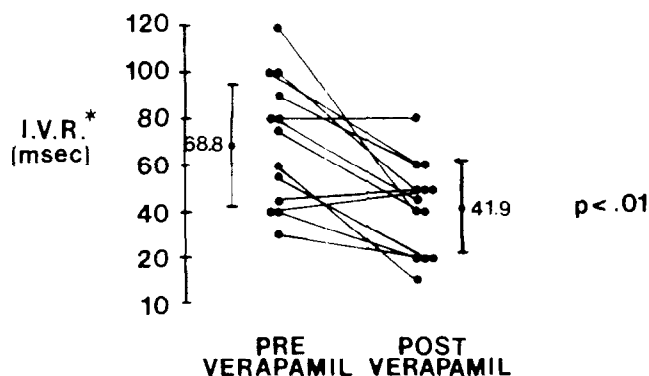
FIGURE 7. Effect of verapamil on isovolumic relaxation time (I.V.R.). IVR was calculated as Q to mitral opening − Q to aortic closure. Values are mean ± standard deviation.

increased LV dimension may result in diminution of LV outflow gradient and end-diastolic pressure. In addition, when septal thickness and posterior wall thickness were adjusted for body size, both measurements appeared to be decreased after verapamil. Despite the limitations of using 1-dimensional echocardiography[24] in assessing septal thickness and muscle mass, the changes in diastolic dimension and relaxation time do not require appraisal of these parameters. Although changes in diastolic dimensions were not documented by cardiac catheterization in this study, they were observed in acute drug studies.[3] Therefore, our data suggest that in pediatric patients and young adults, chronic verapamil therapy may not only increase LV dimension, but also decreases both LV septal and posterior wall thickness.

The electrocardiographic changes in our patients were variable. Six patients showed increases in $S_{V_1} + R_{V_6}$ or RaV_L during verapamil therapy and 7 showed no changes or decreases. This finding contrasts with reports of progressive LV hypertrophy in patients with HC who receive no treatment or propranolol.[25] Although the variability of the electrocardiographic changes in our patients precludes reliable conclusions, the improvement or lack of progression of LV forces in certain patients and the body size–adjusted decrease in LV septal and posterior wall thickness suggests that verapamil may alter the underlying pathophysiologic process causing LV hypertrophy.

Finally, we were encouraged by the absence of side effects with verapamil therapy. No patient complained of abdominal pain, constipation, nausea, palpitations or visual disturbances. No episodes of bradycardia, heart block, hypotension, pulmonary edema or sudden death occurred.

In conclusion, our data suggest that chronic oral verapamil therapy improves symptoms of dyspnea, angina, dizziness, near syncope and syncope. It increases exercise endurance and improves exercise-induced ectopy and ST changes. Oral verapamil treatment was well tolerated and had few side effects in our patients

with HC. Therefore, we recommend verapamil as an effective therapy for HC in the pediatric population.

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