Hypertrophic Cardiomyopathy in Infants: Clinical Features and Natural History

BARRY J. MARON, M.D., ABDUL J. TAJIK, M.D., HERBERT D. RUTTENBERG, M.D.,
THOMAS P. GRAHAM, M.D., GERALD F. ATWOOD, M.D., BENJAMIN E. VICTORICA, M.D.,
J. T. LIE, M.D., AND WILLIAM C. ROBERTS, M.D.

SUMMARY The clinical and morphologic features of hypertrophic cardiomyopathy in 20 patients recognized as having cardiac disease in the first year of life are described. Fourteen of these 20 infants were initially suspected of having heart disease solely because a heart murmur was identified. However, the infants showed a variety of clinical findings, including signs of marked congestive heart failure (in the presence of nondilated ventricular cavities and normal or increased left ventricular contractility) and substantial cardiac enlargement on chest radiograph. Other findings were markedly different from those usually present in older children and adults with hypertrophic cardiomyopathy (e.g., right ventricular hypertrophy on the ECG and cyanosis). Consequently, in 14 infants, the initial clinical diagnosis was congenital cardiac malformation other than hypertrophic cardiomyopathy.

Twelve of the 14 infants who underwent left-heart catherization showed substantial obstruction to left ventricular outflow (peak systolic pressure gradient ≥35 mm Hg). However, unlike older patients with hypertrophic cardiomyopathy, infants with this condition commonly had marked obstruction to right ventricular outflow (35–106 mm Hg) (nine patients); in six patients, the magnitude of obstruction to right ventricular outflow was at least as great as that to left ventricular outflow.

Asymmetric hypertrophy of the ventricular septum relative to the left ventricular free wall was present in the 16 patients who had echocardiographic or necropsy examination. Ventricular septal thickening was substantial in patients studied both before and after 6 months of age (mean 16 mm), indicating that in patients with hypertrophic cardiomyopathy, marked left ventricular hypertrophy may be present early in life and is probably congenital.

The clinical course was variable in these patients, but the onset of marked congestive heart failure in the first year of life appeared to be an unfavorable prognostic sign; nine of the 11 infants with congestive heart failure died within the first year of life. In infants with hypertrophic cardiomyopathy, unlike older children and adults with this condition, sudden death was less common (two patients) than death due to progressive congestive heart failure.

HYPERTROPHIC CARDIOMYOPATHY is a primary disease of cardiac muscle that usually is not recognized clinically until adulthood.1,2 Therefore, most of the clinical and pathologic information regarding this disease is from older children and adults.4-11 Hypertrophic cardiomyopathy does occur in infants, but only single cases or relatively small groups of patients have been reported.7,12-14 Hence, we assembled the clinical, hemodynamic and morphologic features of a large series of patients with hypertrophic cardiomyopathy in whom cardiac disease was identified in the first year of life.

Patients and Methods

The study includes 20 infants with hypertrophic cardiomyopathy evaluated at five institutions: eight patients from the National Heart, Lung, and Blood Institute, five from the Mayo Clinic, three from Vanderbilt University Hospital, three from the University of Utah Primary Children's Medical Center, and one patient from the University of Florida Shands Teaching Hospital and Clinics. Each patient met the following criteria: clinical identification of heart disease in the first year of life; echocardiographic, angiographic or necropsy demonstration of a markedly hypertrophied but nondilated left ventricle in the absence of another cardiac or systemic disease capable of producing left ventricular hypertrophy;10 and absence of maternal diabetes requiring insulin (to avoid confusion with the transient, nonfamilial form of hypertrophic cardiomyopathy that occurs in infants of diabetic mothers17,18).

M-mode Echocardiography

M-mode echocardiography was performed using a 2.25-MHz, 1.25-cm-diameter unfocused Aerotech transducer and a Hoffrel 201 ultrasound receiver interfaced with a Honeywell 1856 strip-chart recorder. The methods of imaging the ventricular septum and posterior left ventricular free wall have been described.19 Left ventricular internal dimensions at end-diastole and end-systole and aortic root and left atrial dimensions were measured echocardiographically in accord with published methods and criteria.20,21
Necropsy Analyses

Ventricular wall thicknesses were measured in the ventricular septum at the point of maximal thickness, usually halfway between the aortic valve and the apex of left ventricle, and in the left ventricular free wall behind the midpoint of the posterior mitral leaflet at a level corresponding to the tips of the mitral leaflets. Trabeculae, papillary muscles and the crista supraventricularis were not included in the measurements of ventricular wall thicknesses. The extent of cardiac muscle cell disorganization in tissue sections of ventricular septum was assessed quantitatively.22,23

Results

Clinical Identification

Each of the 20 infants was a product of a term pregnancy; gestation was complicated by hydramnios in three. Birth weights ranged from 2.4–4.6 kg. Nineteen patients had no significant medical problems during the neonatal period; one patient had seizures associated with hypocalcemia and hypoglycemia of unknown cause. Eleven infants were male and nine were female. Heart disease was identified in each infant during the first year of life (from 1 day to 10 months of age; mean 3 months).

In 14 patients, the initial suspicion of heart disease arose solely because a systolic murmur was detected; the murmurs were usually judged to be ejection murmurs, were grade 2–4/6 and were heard loudest at the fourth left intercostal space or apex. Heart disease was initially identified because of the onset of congestive heart failure in three patients, bradycardia in one patient, and central cyanosis at rest or with crying associated with arterial oxygen desaturation in two patients.

In six infants, hypertrophic cardiomyopathy was correctly diagnosed during the initial clinical evaluation. In the other 14 patients, a cardiac disease other than hypertrophic cardiomyopathy was considered first: pulmonic valve stenosis in three patients, ventricular septal defect in three, cyanotic congenital heart disease in two, congenital mitral valve disease in two,

![ECG images](http://circ.ahajournals.org)
aortic valve stenosis in one patient, left ventricular tumor in one, myocarditis in one, and congenital complete atrioventricular block in one. In seven of these 14 patients hypertrophic cardiomyopathy was correctly diagnosed at ages 10 days to 3 years (median 9 months).

An associated congenital noncardiac anomaly was also identified in four patients: lentiginosis with deafness, Noonan syndrome, tuberous sclerosis with pyloric stenosis and Pierre-Robin syndrome. Clinical necropsy data for the 20 patients are summarized in table 1.

Electrocardiograms

The ECGs were abnormal in each infant. A wide variety of abnormalities was identified (fig. 1), but no ECG pattern was characteristic of the overall study group (table 1). Right ventricular hypertrophy, present in 11 patients, was the most common abnormality. Seven patients had left ventricular hypertrophy and five had diffuse ST-segment and T-wave abnormalities. Four patients had abnormal Q or QS waves. The ECG pattern showed no consistent relation to the hemodynamic state, although five of six patients with left ventricular hypertrophy on the ECG had marked and predominant obstruction to left ventricular outflow.

Chest Radiographic Findings

Heart size on the chest radiograph was larger than normal (cardiothoracic ratio > 0.55) in 19 of the 20 infants, including six of the seven who were asymptomatic. Cardiothoracic ratios ranged from 0.50–0.76 (mean 0.65). Of the eight infants in whom serial radiographs were obtained over a period of 10 months to 6.5 years, heart size was significantly decreased in three, increased in one and unchanged in four.

Hemodynamic, Angiographic and Functional Findings

Cardiac catheterization was performed in 16 infants, 2 weeks to 3.5 years of age. Of the 14 patients who underwent left-heart catheterization, 12 had a left ventricular outflow tract pressure gradient at rest (range 35–120 mm Hg; average 75 mm Hg) (fig. 2, table 1). The two other patients had no left ventricular outflow gradient. One other patient (no. 14), who did not undergo cardiac catheterization, was judged to have no left ventricular outflow tract obstruction based on the absence of systolic anterior motion of the anterior mitral leaflet on the echocardiogram. Twelve patients had right ventricular outflow tract pressure gradients of 10 mm Hg or greater (range 10–106 mm Hg; average 46 mm Hg). In nine of these infants, the right ventricular outflow peak systolic gradient was substantial (35–106 mm Hg). In six infants, the magnitude of obstruction to right ventricular outflow equaled or exceeded that to left ventricular outflow (including patient 1, who had right ventricular outflow tract obstruction only). Left ventricular end-diastolic pressure was elevated in seven infants (range 12–25 mm Hg) and was normal in seven. Right ventricular end-diastolic pressure was elevated (6–20 mm Hg) in 10 infants and normal (< 6 mm Hg) in four.

Left ventricular angiograms were obtained in 13 infants and were abnormal in each (fig. 3). The angiograms showed a variety of configurations in diastole, although no left ventricular appearance was particularly characteristic of the patient group. Mitral regurgitation was judged to be moderate or severe in three infants, mild in two, and absent in eight. In the eight patients who underwent right ventricular angiography, right ventricular outflow tract narrowing was present during systole, and obstruction to right ventricular outflow was shown hemodynamically.

Each of the 16 patients studied by angiography or echocardiography showed evidence of normal or increased left ventricular contractility (ejection fraction 0.60–0.92 by angiography or 0.75–0.90 by echocardiography) (figs. 3C and 3E), including nine who had overt signs of congestive heart failure. However, no patient had evidence of left ventricular dilatation; the left ventricular cavity was assessed to be normal or small by angiography or at necropsy in 11 infants and left ventricular internal diastolic dimension by echocardiography was normal or decreased (15–33 mm)
Table 1. Clinical and Necropsy Data in 20 Patients

<table>
<thead>
<tr>
<th>Age now or at death</th>
<th>Sex</th>
<th>Age heart disease identified</th>
<th>Reason heart disease suspected</th>
<th>Initial clinical diagnosis</th>
<th>Signs/ symptoms</th>
<th>ECG*</th>
<th>Echo†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RVH</td>
<td>PW</td>
</tr>
<tr>
<td></td>
<td>Pt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LVH</td>
<td>Thickness (mm)</td>
</tr>
<tr>
<td>Survivors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 1 yr 4 mo M</td>
<td>2 mo</td>
<td>Murmur</td>
<td>HCM</td>
<td>None</td>
<td>+ 0 +</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td>2 2 yr 9 mo M</td>
<td>2 wks</td>
<td>Murmur</td>
<td>HCM</td>
<td>None</td>
<td>+ 0 0</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>3 2 yr 9 mo M</td>
<td>1 day</td>
<td>Murmur</td>
<td>HCM</td>
<td>None</td>
<td>+ 0 +</td>
<td>22</td>
<td>3.1</td>
</tr>
<tr>
<td>4 3 yr 4 mo M</td>
<td>7 mo</td>
<td>HCM</td>
<td>None</td>
<td></td>
<td>0  + 0</td>
<td>12</td>
<td>1.7</td>
</tr>
<tr>
<td>5 4 yr F</td>
<td>10 mo</td>
<td>Murmur</td>
<td>VSD</td>
<td>None</td>
<td>0 3+ 0</td>
<td>14</td>
<td>23</td>
</tr>
<tr>
<td>7 5 yr 8 mo M</td>
<td>5 mo</td>
<td>Murmur</td>
<td>HCM</td>
<td>Fatigue, lightheadedness, syncope</td>
<td>0  + 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 9 yr 4 mo F</td>
<td>10 days</td>
<td>Murmur</td>
<td>LV tumor</td>
<td>CHF, dyspnea, angina</td>
<td>0  + 0</td>
<td>24</td>
<td>2.1</td>
</tr>
<tr>
<td>9 11 yr 7 mo F</td>
<td>6 wks</td>
<td>Murmur</td>
<td>VSD</td>
<td>CHF</td>
<td>0  + 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 12 yr 5 mo M</td>
<td>9 mo</td>
<td>Murmur</td>
<td>PS</td>
<td>Syncope (one episode only)</td>
<td>+ 0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 1 mo M</td>
<td>4 days</td>
<td>CHF</td>
<td>PS</td>
<td>CHF-sudden death</td>
<td>+ 0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 1 mo M</td>
<td>1 mo</td>
<td>CHF</td>
<td>Congenital MS</td>
<td>CHF</td>
<td>+ 0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 2 mo F</td>
<td>1 day</td>
<td>Bradycardia</td>
<td>Congenital CAVB</td>
<td>CHF</td>
<td>0 0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 2 mo F</td>
<td>1 day</td>
<td>Murmur</td>
<td>HCM</td>
<td>CHF-sudden death</td>
<td>+ 0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 5 mo M</td>
<td>6 wks</td>
<td>Murmur</td>
<td>Congenital MR</td>
<td>CHF</td>
<td>+ 0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 5 mo M</td>
<td>3 wks</td>
<td>Murmur</td>
<td>VSD (&amp; ASD)</td>
<td>CHF</td>
<td>0 0 +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 8 mo F</td>
<td>3 days</td>
<td>Murmur</td>
<td>Valvular PS</td>
<td>CHF-postop death</td>
<td>+ 0 0</td>
<td>13</td>
<td>1.9</td>
</tr>
<tr>
<td>19 11 mo M</td>
<td>10 mo</td>
<td>CHF</td>
<td>Myocarditis</td>
<td>CHF</td>
<td>0 0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 9 yr 2 mo M</td>
<td>9 mo</td>
<td>Valvular AS</td>
<td>None—died of enterocolitis</td>
<td>CHF</td>
<td>0 0 +</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data were obtained from the ECG recorded closest to 1 month of age.
†Data were obtained from the technically best echocardiographic study recorded closest to 2 years of age.
‡Left or right ventricular hypertrophy with "strain" pattern (i.e., with associated ST-segment and T-wave abnormalities).
§Postoperative left ventricular outflow tract gradient recorded in the operating room was zero.
¶Left and right ventricular outflow tract gradients recorded at cardiac catheterization 5 weeks after operation were each 20 mm Hg.
***The infant's father died suddenly at age 30 years, presumably of hypertrophic cardiomyopathy.
††Grading system for magnitude of systolic anterior motion of the anterior mitral leaflet (SAM): from + (slight anterior motion) to 4+ (prolonged contact between anterior mitral leaflet and ventricular septal endocardium, consistent with the presence of marked obstruction to left ventricular outflow††).  
++Performed through aortotomy at age 21 months (body weight 10.5 kg).
§§Performed through left and right ventriculotomies, at age 16 months (body weight 8.1 kg).
¶¶Treated with digitalis briefly, before the diagnosis of hypertrophic cardiomyopathy was made; each patient showed clinical deterioration or lack of improvement while taking digitalis.
Abbreviations: AS = aortic stenosis; ASD = atrial septal defect; CAVB = complete atrioventricular block; CHD = congenital heart disease; CHF = congestive heart failure; EDP = end-diastolic pressure; EF = ejection fraction; TGV = transposition of the great vessels; HCM = hypertrophic cardiomyopathy; LV = left ventricular; LVIDd = left ventricular internal dimension at end-diastole; LVOT = left ventricular outflow tract; LVH = left ventricular hypertrophy; M-M = ventricular septal myotomy and myectomy; MR = mitral regurgitation; MS = mitral stenosis; PS = pulmonary stenosis; PW = posterior left ventricular free wall; RV = right ventricular; RVH = right ventricular hypertrophy; SAM = systolic anterior motion of the anterior mitral leaflet; VS = ventricular septum; VS/PW = ventricular septal-to-posterior left ventricular free wall thickness ratio.
### Table 1. (Continued)

<table>
<thead>
<tr>
<th>Hemodynamics (mm Hg)</th>
<th>Medications</th>
<th>Genomic transmission</th>
<th>Necropsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outflow gradients</td>
<td>EDP</td>
<td>Propranolol Digitalis</td>
<td>Operation</td>
</tr>
<tr>
<td>LVOT</td>
<td>RVOT</td>
<td>LV</td>
<td>RV</td>
</tr>
<tr>
<td>0</td>
<td>37</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>37</td>
<td>35</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>65</td>
<td>10</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>90</td>
<td>18</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>100</td>
<td>2</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>35</td>
<td>45</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>104§</td>
<td>4</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>100</td>
<td>50</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>120</td>
<td>70</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>107¶</td>
<td>106¶</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>0</td>
<td>—</td>
<td>12</td>
<td>—</td>
</tr>
<tr>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>—</td>
<td>21</td>
<td>—</td>
<td>13</td>
</tr>
<tr>
<td>46</td>
<td>—</td>
<td>15</td>
<td>—</td>
</tr>
<tr>
<td>—</td>
<td>85</td>
<td>—</td>
<td>20</td>
</tr>
<tr>
<td>55</td>
<td>95</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>42</td>
<td>64</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>

relative to body surface area in the other nine patients.

**Structural Cardiac Features Identified by Echocardiography and at Necropsy**

Asymmetric hypertrophy of the ventricular septum relative to the posterior left ventricular free wall\textsuperscript{16, 27} (septal-to-free wall thickness ratio ≥ 1.3) was identified in all 16 patients studied by echocardiography or at necropsy (figs. 4 and 5, table 1). The septal-free wall ratio was 1.5 or greater in 13 of these 16 infants (fig. 6). Each of the 16 infants also had a marked increase in absolute ventricular septal thickness. The mean septal thickness was 16 mm (range 8–30 mm) and clearly exceeded the upper limit of normal relative to body surface area, based on normal diastolic or systolic echocardiographic values,\textsuperscript{19} in each infant (fig. 7). There was no direct relation between septal thickness and body surface area. In seven infants who underwent echocardiographic or necropsy examination before 6 months of age, the mean ventricular septal thickness was also 16 mm. However, in the six patients with serial echocardiographic measurements (only one of whom showed clinical deterioration), neither ventricular septal thickness nor septal–free wall thickness ratio changed substantially with age during a follow-up of 9 months to 3 years (fig. 8).

Left atrial dimension measured echocardiographically was mildly increased relative to body surface area in two patients (27 mm and 28 mm) and was normal in seven. Five patients had marked systolic anterior motion of the anterior mitral leaflet (fig. 4), each of whom had left ventricular outflow gradients of 55–100 mm Hg at catheterization. Systolic anterior...
motion was absent or mild in four other patients.

The extent of cardiac muscle cell disorganization in the ventricular septum was assessed quantitatively at necropsy in eight infants. Seven of these patients (five younger than 6 months of age) had marked septal disorganization that occupied more than 5% of the tissue section, consistent with the histologic diagnosis of hypertrophic cardiomyopathy;22, 23 in the remaining patient, 3% of the section was involved (table 1).

Clinical Course and Treatment

Survivors

Ten patients survived during the observation period (mean follow-up of 5.5 years) (fig. 9, table 1). Seven of these 10 patients were asymptomatic when their heart disease was identified and have remained virtually asymptomatic throughout the period of follow-up (mean 3.5 years), although one, patient 10, had a single episode of syncope. Five of the seven asymptomatic patients received propranolol (3 mg/kg/day in each) and one underwent combined ventricular septal myotomy-myectomy28 and resection of right ventricular outflow tract muscle, which resulted in substantial reduction of left and right ventricular outflow obstruction. Three other patients (nos. 7, 8 and 9) were symptomatic at the initial evaluation but improved substantially during the follow-up period, including two who had shown evidence of congestive heart failure; two of these three improved infants became asymptomatic. This improvement was evident after septal myotomy-myectomy in one (patient 7) and after treatment with propranolol (3 and 6 mg/kg/day) in the other two (patients 8 and 9).

Nonsurvivors

Ten patients died during the observation period, including one who died of noncardiac disease (enterocolitis with paralytic ileus) (fig. 9, table 1). The nine patients who died of heart disease had the onset of symptoms and died during the first year of life (age range 1–11 months; median 2 months). Five of these nine patients died of progressive congestive heart failure.
failure, for which they had received digitalis; two other patients with severe heart failure died shortly after operation (resection of right ventricular outflow tract muscle). The remaining two patients (nos. 11 and 14) died suddenly, although each had evidence of congestive heart failure. Patient 11 was under treatment with digitalis for marked heart failure and died unexpectedly at 1 month of age; patient 14, who had relatively mild manifestations of congestive heart failure, died suddenly at 2 months of age despite propranolol therapy (5 mg/kg/day).

The patients who survived and those who died of heart disease did not differ substantially with regard to ventricular septal thickness, outflow tract gradient, end-diastolic pressure, or ECG pattern. For the overall study group, the follow-up period ranged from 3 days to 11.5 years (mean 3.3 years).

Family Studies

Genetic transmission of hypertrophic cardiomyopathy was documented in the families of six infants (table 1). In five of these six families, echocardiographic studies demonstrated genetic transmission of asymmetric septal hypertrophy in one first-degree relative of the index case. In the sixth family, the father of the infant died suddenly and unexpectedly at age 30 years; an autopsy was not performed.

Echocardiographic studies of first-degree relatives (i.e., both parents and two to five siblings) of six additional infants did not show evidence of hypertrophic cardiomyopathy. We could not perform comprehensive echocardiographic studies in relatives of the remaining eight infants; hence, genetic transmission of hypertrophic cardiomyopathy could not be determined definitively in these families.

Discussion

The clinical features and course of infants with hypertrophic cardiomyopathy may be quite variable. For example, although these infants were usually first suspected of having heart disease on the basis of a murmur, they also presented with signs of marked congestive heart failure, or even cyanosis (probably due to right-to-left shunting through a patent foramen ovale in the presence of right ventricular systolic hypertension). Hence, hypertrophic cardiomyopathy in infants may mimic other congenital heart diseases, and its clinical presentation often differs from that usually observed in children and adults with hypertrophic cardiomyopathy.

Indeed, in most of our patients, cardiac diseases other than hypertrophic cardiomyopathy were initially considered (most commonly, pulmonic valve stenosis, cyanotic congenital heart disease, ventricular septal defect, or congenital mitral or aortic valve disease).

Unlike older children and adults with hypertrophic cardiomyopathy, about one-fourth of our
obstructive form of hypertrophic cardiomyopathy (the most common hemodynamic variety of this disease in adults) would be less likely to be identified in infancy because no murmur or only a soft murmur would be present.

Nevertheless, the onset of marked congestive heart failure during the first year of life appeared to be a poor prognostic sign; nine of the 11 patients with this clinical course died, either suddenly, of heart failure or after operation, before 1 year of age. Digitalis was administered to seven of the nine infants who died, including three with obstruction to ventricular outflow, and was ineffective in treating their marked congestive heart failure. The clinical profile of heart failure in these patients occurred in the presence of a non-dilated heart with normal or increased systolic function. Hence, administration of digitalis would seem inappropriate, particularly if obstruction to ventricular outflow is present, and we do not recommend its use in such patients.

The two infants in this study group who had heart failure and survived had received propranolol. Although β blockers such as propranolol theoretically reduce left ventricular outflow obstruction, their negative inotropic effect on ventricular contractility may compromise their therapeutic value in infants with hypertrophic cardiomyopathy and heart failure. Thus, the safest course for infants with hypertrophic cardiomyopathy and severe congestive heart failure may be to administer diuretic agents alone. If this approach is ineffective, cautious use of a β-blocking agent might be warranted.

Infants with hypertrophic cardiomyopathy probably suffer importantly from impairment to ventricular filling. Calcium-channel blockers such as verapamil improve diastolic filling and functional capacity in adults with hypertrophic cardiomyopathy. Therefore, verapamil may be beneficial for treating infants with hypertrophic cardiomyopathy. However, calcium-channel blockers have recognized side effects and should be administered judiciously in such infants.

![Figure 6](image)

**Figure 6.** Assessment by echocardiography (in diastole) or at necropsy of ventricular septal thickness, posterior left ventricular (LV) free wall thickness and septal-free wall thickness ratio in 16 infants. Identity lines define septal-free wall ratios of 1.0, 1.3, 1.5 and 2.0. The echocardiographic data were taken from the technically best study recorded closest to 2 years of age.

Patients became severely symptomatic (and died) with progressive congestive heart failure in the first year of life; only two died suddenly and unexpectedly. However, potential biases in our patient selection preclude definitive conclusions regarding the natural history of hypertrophic cardiomyopathy in infancy. For example, 70% of the patients in this study were identified as having heart disease in infancy solely because of the recognition of a loud heart murmur, indicative of outflow tract obstruction. Hence, patients with the non-

![Figure 7](image)

**Figure 7.** Relation of ventricular septal thickness obtained by echocardiography in diastole (open symbols) or at necropsy (solid symbols) and body surface area (BSA) in 16 infants. Upper limits of normal (shown by the broken and dotted lines) were derived from analysis of echocardiograms from infants without heart disease. The dotted line represents the 95% prediction interval for systolic measurements, with which the septal thicknesses obtained at necropsy are compared. The broken line represents the 95% prediction interval for diastolic measurements, with which septal thicknesses obtained by echocardiography are compared.
Marked obstruction to right ventricular outflow under basal conditions was common in our infants with hypertrophic cardiomyopathy. What causes subpulmonic obstruction in patients with hypertrophic cardiomyopathy is not definitively known; it may be produced by the marked bulging of the hypertrophied ventricular septum\textsuperscript{38} into the relatively small right ventricular outflow tract. Systolic anterior motion of the anterior tricuspid valve leaflet could be another mechanism by which right ventricular outflow tract obstruction occurs in such patients.\textsuperscript{36}

The fact that subpulmonic obstruction is relatively common in infants and young children with hypertrophic cardiomyopathy\textsuperscript{1, 5, 7, 12, 15} but appears to be uncommon in patients who reach adulthood\textsuperscript{4}, can be explained in two ways. First, the right ventricular outflow obstruction present in some infants may resolve spontaneously with growth and aging, as a result of conformational changes in cardiac structure that increase the size of the right ventricular outflow tract. Second, the combined subaortic and subpulmonic obstruction may represent a particularly lethal hemodynamic alteration in infants with hypertrophic cardiomyopathy, predisposing them to premature death, which accounts for the rarity of marked obstruction to right ventricular outflow in adult patients with this disease.

Substantial evidence indicates that hypertrophic cardiomyopathy in children and adults is often genetically transmitted.\textsuperscript{1, 5, 7, 28, 30, 37} Echocardiographic or historical evidence for genetic transmission of hypertrophic cardiomyopathy was found in only six of our 20 infants (30\%); the rest either had no evidence for genetic transmission or insufficient data were available to make this assessment. Therefore, although our data clearly show that genetic transmission may occur in relatives of infants with hypertrophic cardiomyopathy, the true prevalence of genetically transmitted disease in our study population is uncertain. Nevertheless, our findings suggest that in addition to genetically transmitted hypertrophic cardiomyopathy, other etiologically distinct and nongenetic forms of this disease probably occur in infants.

The cardiac structural alterations characteristic of patients with hypertrophic cardiomyopathy can be evident quite early in life and are probably present at birth. Each of the seven patients studied by echocardiography or at necropsy before 6 months of age had substantial ventricular septal hypertrophy. Four of these seven patients, as well as a previously reported stillborn infant,\textsuperscript{13} had an absolute septal thickness of 13 mm or more (range 13–30 mm). However, the fact that the average septal thickness in our infants younger than 6 months of age was 16 mm (compared

\textbf{Figure 8.} Serial echocardiographic assessments, obtained during diastole, of ventricular wall thicknesses (A) and septal–free wall thickness ratios (B) in six infants.
with an average of 21 mm or 26 mm for populations of adult patients with hypertrophic cardiomyopathy studied by echocardiography or at necropsy, respectively) suggests that further thickening of the septum occurs with aging and growth. In addition, five of six patients studied at necropsy before 6 months of age showed marked disorganization of ventricular septal architecture, similar in appearance and extent to that present in older children and adults with hypertrophic cardiomyopathy.

A septal-free wall thickness ratio ≥ 1.3 has been shown at necropsy and by echocardiography to be relatively common in normal neonates and infants with congenital heart malformations other than hypertrophic cardiomyopathy. However, the asymmetry in ventricular wall thicknesses that occurs in such infants should not be confused with the asymmetric left ventricular hypertrophy present in our infants with hypertrophic cardiomyopathy. Infants with “true” hypertrophic cardiomyopathy can be distinguished from other infants with abnormal septal–free wall ratios by three criteria: absence of an associated cardiac lesion capable of producing disproportionate thickening of the ventricular septum; presence of marked absolute ventricular septal thickening; and no substantial decrease in the septal–free wall thickness ratio with increasing age and the persistence of an abnormal septal–free wall ratio (i.e., ≥ 1.3) after 2 years of age.

References


14. Lundquist CB, Amplatz K, Palma SP, Raghib G: Angiographic findings in idiopathic myocardial hypertrophy with right and left ventricular outflow tract obstruction. AJR 93: 315, 1965


34. Epstein SE, Rosing DR: Verapamil: its potential for causing

Verapamil Versus Placebo in Relieving Stable Angina Pectoris

MICHAEL B. PINE, M.D., P. DENNIS CITRON, M.D., DANIEL J. BAILLY, M.D., SAMUEL BUTMAN, M.D., GILBERT O. PLASENícia, M.D., DANIEL W. LANDA, M.D., AND RAYMOND K. WONG, M.D.

SUMMARY Verapamil and placebo were compared in patients with stable, effort-induced angina. Single-blind dose titration (240, 360 and 480 mg/day) preceded a double-blind crossover. Among the 18 patients who completed graded exercise stress tests with reproducible pretreatment effort-limiting angina, exercise duration increased from 348 ± 127 seconds (SD) before treatment to 494 ± 182 seconds after verapamil (p < 0.001), but did not change after placebo. Compared with placebo, verapamil reduced the weekly number of anginal episodes from 4.54 ± 5.03 to 2.44 ± 3.30 (p < 0.05) and reduced nitroglycerin consumption from 3.46 ± 5.30 to 1.55 ± 2.89 tablets per week (p < 0.05). Of 26 patients who completed the single-blind dose titration, 16 were improved (>1 minute) at a dosage of 240 or 360 mg/day. No patient improved (>1 minute) on 480 mg/day who had not already improved on a lower dose, but side effects requiring reduction in dosage occurred in seven patients receiving 480 mg of verapamil per day. Verapamil is an effective antianginal drug that appears most efficacious at a dose of 360 mg/day, but side effects are common at a dose of 480 mg/day.

VERAPAMIL, a derivative of papaverine, blocks slow inward calcium currents in the myocardial conducting system and in smooth muscle cells of systemic and coronary arteries.1 Several studies have shown that verapamil effectively relieves exercise-induced angina if adequate doses are used.2-4 The present study was designed to assess the efficacy of verapamil in treating exercise-induced angina and to evaluate improvement and side effects associated with daily doses of 240, 360 and 480 mg.

Methods and Materials

Thirty male patients with effort-related, stable angina pectoris began the study. The mean age was 57 years (range 45–68 years). The average number of effort-related anginal episodes per week was 7.4 ± 3.8 (SD) by history. Five patients also had occasional pain at rest that recurred without changing significantly in frequency or severity. Seven patients had had angina for less than 1 year, 10 for 1–5 years, and 3 for more than 5 years. Each patient also had at least one of the following: a documented old myocardial infarction (25 patients), coronary artery disease demonstrated by coronary angiography (10 patients), or exercise-induced ST-segment depression of 1.0 mm or greater during the exercise tolerance test given at entry into the study (24 patients). Six patients had residual or recurrent angina after coronary artery bypass grafting. Nine patients received concurrent antihypertensive therapy consisting of diuretics either alone (four patients) or with alpha-methyl dopa (two patients) or prazosin (three patients). None of the patients received digitalis, 8-adrenergic blockers, or long-acting nitrates during the study.

After informed consent was obtained, each patient was evaluated with a complete medical history and physical examination, resting ECG, chest x-ray, complete blood count, urinalysis and blood chemistries. Each patient performed a graded exercise stress test on a stationary bicycle with 25-W increases in work load every 3 minutes until angina pectoris occurred. Each patient was given sublingual nitroglycerin for anginal attacks outside of the hospital and a diary in which to record the number of attacks and the number

From the Departments of Anesthesiology and Medicine, Long Beach Veterans Administration Medical Center, Long Beach, and the University of California, Irvine, California.  
Address for correspondence: Michael B. Pine, M.D., Veterans Administration Medical Center, 3200 Vine Street, Cincinnati, Ohio 45215.  
Received December 3, 1980; revision accepted May 7, 1981. Circulation 65, No. 1, 1982.
Hypertrophic cardiomyopathy in infants: clinical features and natural history.
B J Maron, A J Tajik, H D Ruttenberg, T P Graham, G F Atwood, B E Victorica, J T Lie and W C Roberts

Circulation. 1982;65:7-17
doi: 10.1161/01.CIR.65.1.7

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/65/1/7