Familial Myocardial Disease with and without Obstruction to Left Ventricular Outflow

Clinical, Hemodynamic, and Angiographic Findings

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SUMMARY
Right and left heart catheterization, including selective cineangiocardiology, was performed in 20 of the 33 patients examined in a large Negro family. Fifteen had features compatible with the diagnosis of idiopathic hypertrophic subaortic stenosis. Sudden death has not occurred in this family. Many of the patients were young and were totally unaware of the heart disease, although 11 had symptoms of dyspnea on exertion. A large number of individuals in this family were found to be affected by a familial form of heart disease with similar clinical manifestations, but with a wide spectrum of hemodynamic and cineangiocardiological abnormalities ranging from no obstruction to ventricular outflow and only mild indentation of the ventricular cavity to obstruction and marked narrowing of both ventricular outflow tracts. The patients with obstruction of the left ventricular outflow tract were older than those without obstruction. Therefore, this study provides further evidence that in families with myocardial disease, the presence or absence of outflow tract obstruction is merely a different manifestation of the same basic cardiac disease. This study has also demonstrated distinct left ventricular abnormalities quite early in life suggesting that the disease may be of congenital origin and that obstruction may be a function of the duration of the disease.

ADDITIONAL INDEXING WORDS:
Cardiac hypertrophy  Isoproterenol  Cardiac catheterization  Genetics

DYNAMIC OBSTRUCTION to left ventricular outflow has appeared throughout the literature under a variety of names: functional obstruction of the left ventricle, functional aortic or subaortic stenosis, pseudo-aortic stenosis, muscular subvalvular aortic stenosis, asymmetrical hypertrophy of the heart, obstructive cardiomyopathy, hypertrophic obstructive cardiomyopathy, hereditary cardiovascular dysplasia, diffuse subvalvular aortic stenosis, and idiopathic hypertrophic subaortic stenosis. The excellent monograph by Braunwald and associates has led to wide acceptance of the latter terminology.

In recent years, reports of the familial form of this disease have appeared in the literature with increasing frequency. The diagnosis of familial subaortic stenosis in many of the reported cases, however, has been made by clinical examination or by a history of heart disease or unexplained death in a relative of a patient with the disease. Few hemodynamic and angiographic studies have been
performed in asymptomatic members of a family afflicted with this form of heart disease, even though a significant number of asymptomatic patients have been reported.\(^7,\,10,\,14\text{--}17\) That some of these patients may not have outflow tract obstruction is apparent from the study of Braunwald and associates.\(^13\) These authors reported that outflow tract obstruction could not be demonstrated in some patients whose clinical features were indistinguishable from those of patients with idiopathic hypertrophic subaortic stenosis (IHSS) even though relatives of these patients had the classic features of IHSS. This finding led to the suggestion that the presence or absence of obstruction to left ventricular outflow may not represent a fundamental difference between two diseases.

In the past 2 years, we have evaluated 33 members of a large Negro family, 20 of whom underwent cardiac catheterization and cineangiographic studies and 15 of whom were found to have cardiac abnormalities, some of which were the distinctive hemodynamic and cineangiographic features of IHSS. It is the purpose of this report to present the findings in this family and to provide further evidence that the presence or absence of outflow tract obstruction in patients with this type of heart disease does not represent two different diseases. Distinct abnormalities were found in some of the younger asymptomatic members of this family, suggesting a congenital origin of this disorder. Furthermore, to the best of our knowledge, this is the first report of the occurrence of a familial form of IHSS in a Negro family.

**Methods**

A complete clinical evaluation, including chest x-rays, electrocardiogram, phonocardiogram, external carotid arterial pressure tracings, and apex cardiograms, was made in 27 of 33 Negro members of a large kindred comprising four generations. Right and left heart catheterization was performed in 20 of the patients. Simultaneous pressure recordings across both ventricular outflow tracts were obtained during rest, exercise, isoproterenol (Isuprel) infusion (2 \(\mu\)g per minute for 5 minutes), and during the Valsalva maneuver. Cardiac output and index were determined during rest, exercise, and isoproterenol infusion by the direct Fick method or indicator-dilution technique, or both. Cineangiography with selective injection into the left ventricle, right ventricle, and ascending aorta was made on all 20 patients. Blood was drawn for genetic studies in 26 patients.

**Results**

Fifteen members were found to have significant cardiac abnormalities, although only six had features distinctive of IHSS. One of these 15 members (II-3) had heart catheterization and cardiac surgery at another hospital. Postmortem examination performed 4 days postoperatively revealed pathological changes compatible with IHSS. Another patient (II-6), not included in the 15 affected patients, died in another hospital with congestive heart failure due to heart disease of unknown etiology. Thirteen of the 15 affected patients had hemodynamic or cineradiographic abnormalities, or both, while the remaining two patients had clinical evidence of heart disease although catheterization studies were not performed. Thirteen of the 15 members affected with heart disease were divided into two groups based on the findings at cardiac catheterization: group I consisting of six patients with evidence of left ventricular outflow tract obstruction and group II consisting of seven patients without left ventricular outflow tract obstruction. Two patients had clinical evidence of heart disease but could not be placed in either group since they were not catheterized. Eighteen of the 33 members were asymptomatic and had no abnormal clinical findings. Seven of these underwent cardiac catheterization and contrast studies, all of which were within normal limits.

**Genetic Analysis**

Figure 1 includes all pertinent relationships. Blood groups (ABO, Rh, MNS, Kell, Duffy and Pand Leins), determined on all family members examined, revealed no evidence of linkage or parental exclusion.

Table 1 summarizes normal and affected family members by sex and sibship. There is no significant deviation from the expected values of 0.5 for these two parameters.
Figure 1
Pedigree of family.

Table 1
Segregation of Normal and Affected Family Members by Sex and Sibship*

<table>
<thead>
<tr>
<th>Sibship</th>
<th>Male</th>
<th></th>
<th>Female</th>
<th></th>
<th>Total</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Affected</td>
<td>Normal</td>
<td>Affected</td>
<td>Normal</td>
<td>Affected</td>
</tr>
<tr>
<td>II 1-12</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>III 1-5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>III 17-27</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>III 28-30</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>III 31</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>III 51-55</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>IV 1-3</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>IV 16</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total observed</td>
<td>12</td>
<td>9</td>
<td>10</td>
<td>7</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>Expected</td>
<td>10.5</td>
<td>10.5</td>
<td>8.5</td>
<td>8.5</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>$X^2$</td>
<td>0.45 ($P = 0.50$)</td>
<td>0.53 ($P = 0.47$)</td>
<td>0.95 ($P = 0.33$)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Based on the genetic analysis of 38 members in this family (only 33 members were examined).

The age distribution of the patients with heart disease is compared with those normal for the trait at the time of ascertainment in those at risk (fig. 2). There is an excess of normals in those less than 10 years of age ($X^2 = 6.4, P<0.02$). Only one affected patient was detected in this age group, suggesting age dependency for expression of the trait.

Age and Sex

The 33 members examined ranged in age from 3 to 44 years (average, 17 years) (fig. 2). Fifteen (45%) of the 33 patients were considered to be affected with heart disease (table 2). Fifteen (45%) were female and 18 (55%) were male. The 15 patients with heart disease ranged in age from 8 to 44 years.
Table 2

Clinical, Electrocardiographic, and Radiographic Findings in Fifteen Affected Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Cardiac Findings</th>
<th>ECG</th>
<th>Chest x-ray</th>
<th>Functional class</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SM (grade)</td>
<td>S4</td>
<td>S5</td>
<td>Thrill</td>
</tr>
<tr>
<td>Group I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-1</td>
<td>42</td>
<td>F</td>
<td>x</td>
<td>IV/VI</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>II-3</td>
<td>43</td>
<td>M</td>
<td>x x x x</td>
<td>IV/VI</td>
<td>x</td>
<td>x</td>
<td>AF</td>
</tr>
<tr>
<td>II-12</td>
<td>32</td>
<td>M</td>
<td>x</td>
<td>IV</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>III-17</td>
<td>19</td>
<td>M</td>
<td>x x x</td>
<td>III/VI</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>III-22</td>
<td>13</td>
<td>F</td>
<td>x</td>
<td>IV/VI</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>III-29</td>
<td>21</td>
<td>M</td>
<td>x</td>
<td>IV/VI</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Group II</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-8</td>
<td>44</td>
<td>F</td>
<td>x</td>
<td>III/VI</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>III-1</td>
<td>27</td>
<td>F</td>
<td>x</td>
<td>III/VI</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>III-4</td>
<td>20</td>
<td>M</td>
<td>x</td>
<td>III</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>III-20</td>
<td>16</td>
<td>M</td>
<td>x</td>
<td>III/VI</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>III-23</td>
<td>11</td>
<td>F</td>
<td>x</td>
<td>III/VI</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>III-24</td>
<td>10</td>
<td>M</td>
<td>x</td>
<td>III/VI</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>III-26</td>
<td>8</td>
<td>M</td>
<td>x</td>
<td>III/VI</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Not catheterized</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>III-2</td>
<td>24</td>
<td>F</td>
<td>x</td>
<td>III/VI</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>III-28</td>
<td>24</td>
<td>M</td>
<td>x</td>
<td>IV/VI</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>10</td>
<td>9</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations: x = finding present; 1 = dyspnea; 2 = chest pain; 3 = dizziness; 4 = syncope; SM = systolic murmur; S4 = atrial sound; S5 = early ventricular filling sound; S6 = second heart sound; NSR = normal sinus rhythm; LVH = left ventricular hypertrophy; AF = atrial fibrillation; LAE = left atrial enlargement; and PSD = poststenotic dilatation.
(average, 24 years). The average age of the patients in group I was 30 years; that of the patients in group II was 19 years. Of the 15 patients affected, nine were male and six were female giving a male to female ratio of 3 to 2. Four of the six patients in group I were male and four of the seven patients in group II were male.

**Symptoms**

Only 11 of the 15 affected patients were symptomatic: five in group I, four in group II, and both patients who had clinical evidence of heart disease but were not catheterized (table 2). Dyspnea on exertion was the most common symptom, being found in all 11 symptomatic patients. Symptoms other than dyspnea occurred only in the group I patients and consisted of exertional dizziness in three, syncope in two, and symptoms of angina pectoris in two patients. When placed in a functional classification (New York Heart Association), four patients were in class I, 10 were in class II, and one was in class IV.

**Physical Examination**

The results of the physical examination are presented in table 2. A systolic ejection murmur was present in only 10 of the 15 affected patients; this was maximal along the lower left sternal border and apical area and occurred in five patients in group I, three patients in group II, and both of the noncatheterized patients. The systolic murmur was of grade III/VI intensity, or greater, in each patient. A systolic thrill was present in five patients, four of whom were in group I. It is of interest that the systolic murmur was of variable intensity during several examinations of a single patient which may explain the absence of a systolic murmur in some of the patients examined only once. A diastolic murmur was not heard in any patient. An atrial sound (S₄) was heard and recorded on a phonocardiogram in nine patients, four in group I, three in group II, and both noncatheterized patients. An early diastolic filling sound (S₂) was heard and recorded in seven patients, all of whom were less than 20 years of age and who showed no clinical evidence of cardiac decompensation. All 15 patients had physiological splitting of the second heart sound, and a systolic ejection sound was not heard or recorded in any patient.

**External Carotid Pulse Tracing and Apex Cardiogram**

Only five patients in the present series, all in group I, had external carotid pulse tracings and apex cardiograms which could be considered characteristic of IHSS. The configuration of the external carotid pulse tracing and the apex cardiogram was normal for all seven patients in group II who had no evidence of significant narrowing of the left ventricular outflow tract in the cineangiograms. The external carotid pulse tracing and apex cardiogram were normal in both of the noncatheterized patients.

**Electrocardiogram**

Electrocardiographic abnormalities were found in only five patients (table 2). Left ventricular hypertrophy (LVH) (fig. 3) was present in four patients, two in group I, one in group II, and one of the noncatheterized patients. All four patients complained of dyspnea. One patient (II-3) in group I had atrial fibrillation and was the patient most severely disabled by his heart disease, even though electrocardiographic criteria for left ventricular hypertrophy were not present. The other 14 patients had normal sinus rhythm and had no complaints of paroxysmal tachycardia. Ten patients had normal electrocardiograms, three in group I, six in group II, and one of the noncatheterized patients. The mean resultant electrical axis of the QRS complex in the frontal and horizontal planes was normal in all 15 patients.

**Chest X-rays**

Only eight of the 15 affected patients had roentgenographic evidence of cardiomegaly, and five of these patients were in group I (table 2). Poststenotic dilatation of the aorta was present in only one patient (III-24). Roentgenographic evidence of left atrial enlargement was present in two patients while the pulmonary vasculature was normal in all 15 patients. Valvular calcification was not
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observed in any patient by fluoroscopic examination.

Hemodynamic Studies (Table 3)

Of the 20 patients catheterized, seven had normal cardiac hemodynamics without evidence of obstruction to outflow in either ventricle during rest, exercise, isoproterenol infusion, or the Valsalva maneuver. There was no evidence of intracardiac shunt by oximetric studies, indicator-dilution studies, or selective cineangiography. The cardiac output and cardiac index were normal in each patient. The pressure response in the left ventricle and systemic artery following a premature contraction was also normal in all of the seven patients. Selective cineangiography with injection into the left ventricle, right ventricle, and ascending aorta also yielded normal results in all seven patients.

Figure 3

Electrocardiogram on patient III-29 showing left ventricular hypertrophy.

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Thirteen of the 20 catheterized patients had distinct hemodynamic or cineangiocardio- graphic abnormalities, or both. Two of the 13 affected patients, one in group I and one in group II, had mild resting systolic pressure gradients across the right ventricular outflow tract. The infusion of isoproterenol increased this pressure gradient in both of these patients and produced a pressure gradient in four others, two in group I and two in group II. In each instance, the pressure gradient was isolated within the body of the right ventricle. The resting pulmonary artery pressure was elevated in only three patients, all of whom were in group I. The resting mean pulmonary capillary wedge pressure was elevated in four patients, all in group I. There was no measurable pressure gradient across the left ventricular outflow tract in any of the 13 affected patients at rest. However, following the infusion of isoproterenol in 12 patients, a mid or late systolic pressure gradient, ranging from 15 to 75 mm Hg, was observed in five patients. The resting left ventricular end-diastolic pressure (LVED) was elevated in five patients, four of whom were in group I. A significant increase in left ventricular end-diastolic pressure during isoproterenol infusion was observed in only two patients, both of whom were in group I. The resting cardiac output was normal in 12 patients and was decreased in only one (II-3). Four patients, each of whom was in group I, exhibited a decreased arterial pulse pressure in the beat following a premature ventricular contraction.
Cineangiographic Studies (Table 4)

All 13 affected patients had demonstrable abnormalities in the configuration of the left ventricle which ranged from a mild indentation on the medial aspect of the left ventricle in the frontal projection to marked narrowing of the left ventricular outflow tract (fig. 4). Five patients had marked narrowing of the left ventricular outflow tract, each of these patients being in group I. In addition, three of the patients in group I had marked narrowing of the right ventricular outflow tract. Mitral regurgitation was noted in four patients, all in group I. The size of the left ventricular chamber was normal in diastole in each of the 13 patients and there was no evidence of aortic insufficiency or valvular calcification. In addition, the aortic valve appeared to be normal in each patient. While obstruction to ventricular outflow was not demonstrated in group II patients, the configuration of the left ventricle was distinctly abnormal in each. This consisted of a globular-shaped left ventricle with a distinct indentation of varying severity on the medial aspect of the left ventricle which was considered due to septal hypertrophy. This finding is apparent in the cineangiograms presented in figure 4 (III-23 and III-26). One of the most striking cineangiographic findings was the presence of moderate to marked enlargement of the coronary arteries (fig. 5) in seven patients, five of whom were in group I.

Comment

The 13 members of this family who were found to be affected with heart disease at the time of cardiac catheterization could be divided into two distinct groups based on
Table 4

Cineangiocardiographic Studies in Thirteen Affected Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Degree of outflow narrowing</th>
<th>LA size</th>
<th>MI</th>
<th>Coronary arteries</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LV</td>
<td>RV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-1</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>II-3</td>
<td>+++</td>
<td>0</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>II-12</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>III-17</td>
<td>++</td>
<td>+++</td>
<td>0</td>
<td>Absent</td>
<td>+++</td>
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<tr>
<td>III-22</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>III-29</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

| Group II | |
| II-8     | + | 0 | 0 | Absent | +++               | Globular LV; large LCA; very small end-systolic LV residual |
| III-1    | + | 0 | 0 | Absent | 0                | Hyperactivity of the anterior portion of the LV outflow tract; mild indentation on medial aspect of LV |
| III-4    | + | 0 | 0 | Absent | 0                | Very small end-systolic LV residual with mild indentation of medial aspect of LV |
| III-20   | ++ | 0 | 0 | Absent | +++              | Indentation on medial aspect of LV in frontal projection; large LCA |
| III-23   | + | 0 | ++ | Absent | 0                | Globular LV; enlarged LA; mild indentation on medial aspect of LV |
| III-24   | ++ | 0 | 0 | Absent | 0                | Globular LV; mild poststenotic dilatation of ascending aorta; moderate indentation on medial aspect of LV |
| III-26   | ++ | + | 0 | Absent | 0                | Globular LV; moderate indentation on medial aspect of LV |

Abbreviations: LV = left ventricle; RV = right ventricle; LA = left atrium; LCA = left coronary artery; MI = mitral insufficiency; 0 = normal; + = mild; ++ = moderate; +++ = marked.
the hemodynamic and cineangiocardiographic findings. Group I consisted of six patients in whom systolic pressure gradients could be induced across the left ventricular outflow tract by the administration of isoproterenol and in whom outflow tract narrowing could be demonstrated by contrast studies. Three of these patients also developed pressure gradients across the right ventricular outflow tract during infusion of the sympathomimetic amine. In four of these patients, the arterial pulse pressure decreased in the beat following

![Figure 4](http://circ.ahajournals.org/)

**Figure 4**

Selective cineangiograms of the left ventricle in four patients. Note the more advanced degree of narrowing of the left ventricular outflow tract in the older patient (II-1). The younger patients (III-23 and III-26) show only a mild to moderate indentation of the medial aspect of the left ventricle which is globular in configuration. Narrowing of the right ventricular outflow tract is also shown (III-17). All frames are shown in systole.

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Selective cineangiogram of the left ventricle in patient II-3. Note the narrowing of the left ventricular outflow tract and large left coronary artery (arrow).

the premature ventricular contraction. Therefore, although pressure gradients at rest were not observed across the left ventricular outflow tract in these patients, the diagnosis of idiopathic hypertrophic subaortic stenosis seems unequivocal. In contrast, the remaining seven members of this family who underwent cardiac catheterization and were found to have manifestations different from those described above were arbitrarily placed in group II. A systolic pressure gradient could not be demonstrated across the left ventricular outflow tract at rest or during isoproterenol infusion in any of these seven patients. However, three of the seven did develop gradients across the right ventricular outflow tract during administration of isoproterenol, a finding reported previously in patients with IHSS. In none of these seven patients was an abnormal response to a premature ventricular contraction observed. While cineangiographic studies in these seven patients did not reveal evidence of outflow tract obstruction in either ventricle, distinct abnormalities in the configuration of the left ventricle were noted in each patient. In general, this abnormality consisted of a normal-sized, globular-shaped left ventricle with an indentation on the medial aspect of the left ventricular cavity, apparently resulting from hypertrophy of the interventricular septum. This finding is strikingly similar to that reported by Braunwald and Aygen in patients with idiopathic myocardial hypertrophy as well as in patients with IHSS. In addition, two of the patients had enlarged coronary arteries which has also been reported in patients with IHSS.

The patients in group II are remarkably similar to the patients with idiopathic myocardial hypertrophy without congestive heart failure or obstruction to blood flow described by Braunwald and Aygen. It is of interest, that in this latter study, relatives of patients with idiopathic myocardial hypertrophy were found with the classic features of idiopathic hypertrophic subaortic stenosis. This led the authors to suggest that the presence or absence of obstruction to ventricular outflow may not reflect a fundamental difference between two diseases. A large number of individuals in the present family were found to be affected with a familial form of heart disease whose clinical manifestations were quite similar. However, the hemodynamic and cineangiographic findings varied from no obstruction to ventricular outflow and only mild medial indentation of the ventricular cavity to marked obstruction and narrowing of both ventricular outflow tracts. Between these two extremes were patients with only right-sided ventricular obstruction while others had only left-sided ventricular obstruction. Those patients with left ventricular outflow tract obstruction generally were the older patients studied, averaging 30 years in age, while those without obstruction averaged only 19 years in age. Only one of the patients in whom obstruction could be produced was less than 18 years of age while four of the patients without obstruction were less than 18 years of age. The results of this study, therefore, provide further evidence that in families with myocardial dis-

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ease, the presence or absence of outflow tract obstruction merely represents different manifestations of the same basic cardiac disease. This study has also demonstrated distinct left ventricular abnormalities quite early in life. This observation suggests that the disease may be of congenital origin and that the occurrence of obstruction may be a function of the duration of the disease. Longitudinal studies of the patients in this family will be necessary to confirm or refute this suggestion.

A comparison of some of the reported series of this type of familial heart disease shows that equal sex distribution is the most common occurrence (table 5). The average age of the patients in the 10 compared series ranged from 19 to 34 years, with the exception of the three pediatric cases by Wood and associates.23 The present series represents the first report of the familial form of this disease in Negroes, although the nonfamilial form has been reported in Negroes.13, 24 Although sudden death has been a prominent feature in Caucasian patients reported, it has not occurred in any of the members of this Negro family. Only 11 of the 15 Negro patients had symptoms, an incidence which conforms with most other familial studies. This is probably the result of early diagnosis as a result of seeking out asymptomatic individuals before their disease becomes manifest since the four asymptomatic patients were the youngest in the present series (ages 8 to 13 years). The absence or changing intensity of systolic murmurs, or both, in this disease is well known. Although hemodynamic and cineangiocardiographic studies have been performed on most of the reported patients with the nonfamilial form of IHSS, table 5 indicates that these studies have not been done in many of the reported cases of the familial form of this disease.

The post premature contraction response of the direct arterial pressure pulse, as described by Brockenbrough and associates,25 was found in only four of our patients, all in group I. The finding of a normal arterial response in

Table 5

| Table 5 |

Comparison of Different Series of Familial Heart Disease (IHSS)

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<tbody>
<tr>
<td>Patients affected</td>
<td>6 8 9 7 9 30* 3 12 10 15</td>
<td>Male</td>
<td>2 6 9 3 4 18 2 5 4 9</td>
<td>Female</td>
<td>4 2 0 4 5 12 1 7 6 6</td>
<td></td>
<td></td>
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<tr>
<td>Average age (yr)</td>
<td>26 28 26 20 19 25 7 23 34 24</td>
<td>Race</td>
<td>Cau Cau Cau Cau Cau Cau Cau Cau Cau Negro</td>
<td></td>
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<tr>
<td>Dead</td>
<td>3 8 6 3 3 15 1 4 9 1</td>
<td>Sudden death</td>
<td>3 7 3 3 2 8 0 3 9 0</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>No. of patients with symptoms</td>
<td>2 4 6 2 4 23/30 3 7 8 11</td>
<td>Systolic murmur present†</td>
<td>3/3 3/6 8/9 5/5 5/8‡ 15/20§ 3/3 9/9 5/5 10/15</td>
<td>Abnormal ECG†</td>
<td>3/3 4/4 3/5 3/5 6/8 19/20** 3/3 6/6 4/6 5/15</td>
<td>Cardiomegaly on chest x-rays†</td>
<td>2/3 1/1 2/4 3/5 7/8 15/20 3/3 3/6 3/3 7/15</td>
<td>Hemodynamic studies</td>
<td>0 0 2 2 0 0 2 1 0 13</td>
</tr>
</tbody>
</table>

*Only 20 of the 30 patients were examined (10 were deceased).
†Refers to the abnormal finding in relation to the number of patients examined for the finding.
‡Four of the five patients also had a diastolic murmur.
§Seven of the 15 patients also had a diastolic murmur.
**Eight of the abnormal ECGs had only nonspecific ST-T changes.
the beat following a premature contraction in this disease in patients without any or with only minimal resting pressure gradients has been documented by others.\textsuperscript{13, 26} Wigle and associates\textsuperscript{27} stated that the classic arterial pulse (rapid upstroke time, midsystolic trough, and late systolic bulge with a taller percussion than tidal wave), in the presence of a demonstrated pressure gradient across the left ventricular outflow tract, is diagnostic of muscular outflow obstruction of the left ventricle. One patient, the proband (II-12), developed the classic response following a premature contraction, and during sinus rhythm exhibited pulsus alternans in the left ventricular pressure pulse (fig. 6). According to Braunwald and associates,\textsuperscript{13} pulsus alternans of the left ventricular pressure pulse is not uncommon in patients with IHSS.

The present family again demonstrates the usefulness of utilizing the genetic approach for the study of specific cardiovascular syndromes. Steady progress has been made in recent years in the delineation of genetic disorders affecting the cardiovascular system whose heritability component is high. McKusick\textsuperscript{28} summarized these disorders recently. The present family, in whom catheterization studies were performed in 20 individuals, is the largest family in whom the clinical condition has been ascertained with a high degree of precision. Clearly, the expressivity of the trait varies from a lesion responsible for death to individuals whose clinical condition is normal. Normal is used here in the context of a mild functional murmur in an individual in whom it was not considered justifiable to perform complete evaluation including cardiac catheterization (for example, sibship III-51-55). While it is possible that some of those

![Figure 6](image_url)

*Figure 6*

Simultaneous left ventricular pressure, brachial artery pressure, and electrocardiogram in patient II-12. Note the diminution of the arterial pulse with accentuation of the left ventricular-arterial gradient following a premature ventricular contraction (PVC) and the pulsus alternans of the left ventricular pressure pulse with the return to sinus rhythm. Observe that the difference between the peak left ventricular pressure (arrow) and the notch on the upstroke of the left ventricular pressure pulse represents the left ventricular outflow pressure gradient, which occurs in late systole. During the recording of these pressures, the catheter tip was placed in the inflow tract of the left ventricle. (Tracings have been retouched.)
individuals indicated as normal in figure 1 carry the gene, they have been classified as normal in the absence of definite hemodynamic and cineangiocardio-graphic confirmation. As seen in table 1, the sexes are equally affected and there is no disturbance in the segregation ratio of 0.5 expected in the case of autosomal dominant inheritance. Penet-

rancse seems to be complete although it is possible that those individuals at risk, but not catheterized, might on later study prove to be affected. It is impossible to determine the age of onset of the cardiovascular lesion of this disease since the criteria for affected patients are mainly one of abnormality in cardiovascular hemodynamics and cineangiocardio-

graphic findings at catheterization. Since this is a large family, the ages at the time of examination were plotted by decades (fig. 2). There is a statistically significant excess of unaffected young children of affected parents. It is possible that, if catheterized, some of these members would demonstrate hemodynamic and cineangiocardio-graphic evidence of this disease. However, in the absence of clinical manifestations of this disease, catheterization was not considered justifiable. The variation in affected family members, even when described at the time of examination without respect to the age of onset of clinical sympto-

matology, adequately describes a trait whose expressivity is influenced by age.

Acknowledgment

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