Left Ventricular Hypertrophy and Morphology in Familial Hypertrophic Cardiomyopathy Associated With Mutations of the Beta-Myosin Heavy Chain Gene

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Objectives. The purpose of this study was to determine the spectrum of left ventricular hypertrophy and ventricular morphology in adults with hypertrophic cardiomyopathy due to mutations of the beta-myosin heavy-chain gene.

Background. Although echocardiography is an important test in diagnosing hypertrophic cardiomyopathy, the lack of an independent diagnostic criterion has been an obstacle in determining the full echocardiographic spectrum of this disease. Mutations in the beta-myosin heavy-chain gene occur in approximately 50% of familial cases; in members of families with a known mutation, the diagnosis can be made with certainty.

Methods. Echocardiograms from 39 genetically affected and 30 genetically unaffected adult family members over age 16 years from 10 families were analyzed. Left ventricular wall thickness was measured at 10 separate locations, and the presence of systolic anterior motion of the mitral valve, right ventricular hypertrophy, and left ventricular morphology was evaluated independently by three separate observers without knowledge of the genetic diagnosis.

Results. The mean maximum v.11 thickness in the genetically affected group was 24 ± 8 mm (range 11 to 40), compared with 11 ± 2 mm (range 7 to 16) in the unaffected group (p < 0.0001). Systolic anterior motion of the mitral valve or chords tendineae with or without leaflet-septal contact was present in 62% of the affected group and in none of the unaffected group. Seventy-seven percent of patients in the affected group had a septal/free wall ratio ≥ 1.3 compared with 6% in the unaffected group, with a septal/posterior wall ratio ≥ 1.3 associated with only a 55% probability of being affected.

Conclusions. The two-dimensional echocardiographic spectrum of hypertrophic cardiomyopathy in a genetically defined adult population is broad. Previous echocardiographic criteria may be too strict to diagnose the disease in some patients who are genetically affected and therefore at risk for adverse events related to the disease. Ultimately, genetic testing may supersede echocardiography in diagnosing hypertrophic cardiomyopathy.

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Since the initial clinical description of hypertrophic cardiomyopathy, the criteria for diagnosis of the disease have reflected the available diagnostic modalities (1). At present, two-dimensional echocardiography is believed to provide the most information about morphologic and hemodynamic features of the disease (2–6). A major obstacle in determining the full echocardiographic spectrum of abnormalities in hypertrophic cardiomyopathy has been the lack of an independent diagnostic criterion, and previous studies that have examined echocardiographic manifestations of hypertrophic cardiomyopathy have generally based the diagnosis itself on echocardiographic criteria, making an accurate assessment of the full spectrum of echocardiographic features and their frequencies impossible.

Recently, the genetic basis for hypertrophic cardiomyopathy in many families has been localized to the cardiac beta-myosin heavy chain gene on chromosome 14 (7–10). Missense mutations in the beta-myosin heavy chain gene are responsible for hypertrophic cardiomyopathy in approximately 50% of families studied (11,12). Nine missense mutations of the beta-myosin heavy-chain gene have been identified, some of which are present in more than one family (12–14). In families with a proved mutation of this gene, members can be genotyped with certainty. This study examines the spectrum of ventricular hypertrophy and other...
morphologic features in adults over age 16 years who are genetically at risk for hypertrophic cardiomyopathy utilizing genotype as the diagnostic criterion for determining affected status.

Methods

Subjects. Seventy-four persons over age 16 years from 10 families who participated in the hypertrophic cardiomyopathy genetics studies and in whom genetic analyses were performed were screened for inclusion in the study. The investigational protocol was approved by the Institutional Review Board, and all subjects provided informed consent. Three subjects were excluded because of poor quality echocardiograms, as were two subjects who had undergone previous myomectomy, leaving 69 for analysis. All subjects included in the study were considered genetically at risk for the disease; that is, they had a known affected parent or sibling. Thirty-nine subjects were genetically affected, and 30 were genetically unaffected, as determined by genetic studies described later. One of the unaffected and none of the affected cohort had a history of hypertension. None of the subjects included in the study were known to have aortic valve disease.

Echocardiographic methods. Echocardiograms were performed at three separate institutions utilizing standard echocardiographic systems. All analyzed studies contained standard two-dimensional echocardiographic views: parasternal long axis, parasternal short-axis at the mitral valve and papillary muscle levels, apical four- and two-chamber and subcostal.

Two-dimensional echocardiographic measurements. All echocardiographic measurements were performed in a core laboratory, with the examiner performing the analysis without knowledge of the genetic diagnoses. End-diastolic left ventricular wall thickness measurements were obtained at 10 separate locations from the parasternal short- and long-axis views; measurements from three separate beats for each location were averaged. Ventricular wall thickness for the anterior, lateral free wall, posterior free wall and inferior walls in the parasternal short-axis view were obtained at both the mitral valve and papillary muscle levels. Septal and posterior wall thickness and left ventricular end-diastolic and end-systolic diameter measurements were also obtained from the parasternal long-axis view. To avoid off-axis measurements, measurements in the short axis were made only when the cavity appeared circular (2).

Qualitative features. Qualitative two-dimensional echocardiographic features were evaluated independently by three echocardiographers who were unaware of the genetic diagnoses. These features included the presence or absence of systolic anterior motion of the mitral valve, the presence or absence of right ventricular hypertrophy, the location of predominant hypertrophy and ventricular morphology. Systolic anterior motion of the mitral valve was classified by each observer as none, chordal only or involving the anterior mitral leaflet. It was considered present if anterior movement of the mitral valve leaflets during systole could be visualized by two-dimensional echocardiography and did not require the presence of full leaflet-septal contact. Right ventricular hypertrophy was considered present if right ventricular free wall thickness in the subcostal view exceeded 7 mm (15). The pattern of left ventricular hypertrophy was classified according to the method of Maron et al. (16) as 1) no hypertrophy, 2) pred-minantly anterior septal hypertrophy, 3) diffuse concentric hypertrophy, 4) hypertrophy of the anterior and posterior septum with sparing of the free wall, or 5) hypertrophy of the anterolateral free wall, apex or posterior septum (16). Ventricular morphology was classified as 1) normal, 2) hypertrophied with reversed septal curvature, 3) hypertrophied with proximal septal bulge, or 4) hypertrophied with normal shape (Fig. 1) (17).

Echocardiographic data analysis. The maximal wall thickness from any location was determined. In addition, a septal/posterior wall ratio was obtained from the ratio of septal/posterior wall thickness in the parasternal long-axis view, the short-axis view at the mitral valve level or the short-axis view at the papillary muscle level. We devised an index of ventricular asymmetry based on the variance of the mean wall thickness measurements in the short-axis views, with a perfectly symmetric ventricle having a wall thickness variance of zero. Wall thickness variance was calculated at both the mitral valve and papillary muscle levels by the following formula:

\[ \text{Wall thickness variance} = \frac{\sum(x - \bar{x})^2}{4} \]

where \( x \) is the wall thickness for each of four wall thickness measurements in the short-axis view at the appropriate level.

Genetic analysis. Genotypic assessment was performed by polymerase chain reaction, as previously described (12).
Individual subjects were determined to be genetically affected or unaffected on the basis of the presence or absence of a missense mutation of the beta-myosin heavy chain gene. The distribution of missense mutations in the families included in this study is shown in Table 1.

Statistical analysis. Differences in mean values between affected and unaffected cohorts were compared with the Student t test for continuous measured variables when tests for normality were satisfied; the Wilcoxon rank-sum test was used for continuous variables for data that were not normally distributed or could not be easily transformed. The chi-square test was applied to categoric variables. Univariate logistic regression analyses were used to derive the probability of affected status on the basis of maximal wall thickness or septal/posterior wall ratio. In addition, multivariate logistic regression analyses were used to determine whether maximal wall thickness, septal/posterior wall ratio, age, wall thickness variance or right ventricular hypertrophy were independently predictive of affected status.

Interobserver agreement. There was complete agreement among all three observers for qualitative features in 92% of patients for systolic anterior motion, 130% of patients for right ventricular hypertrophy, 90% of patients for ventricular morphology and 88% of patients for location of hypertrophy. There was only one instance of complete disagreement among three observers in the location of hypertrophy; this occurred in an affected subject with a maximal wall thickness of 35 mm and extensive hypertrophy.

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Table 2. Wall Thickness Measurements at Various Locations in 69 Subjects

<table>
<thead>
<tr>
<th></th>
<th>Unaffected Group (n = 30)</th>
<th>Affected Group (n = 39)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral valve level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anteroseptal</td>
<td>11 ± 1.8; 9-15</td>
<td>20 ± 7.1; 9-31</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Lateral</td>
<td>9 ± 1.7; 7-15</td>
<td>12 ± 4.5; 6-30</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Posterior</td>
<td>8 ± 1.3; 5-10</td>
<td>11 ± 4.4; 6-30</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Inferior</td>
<td>8 ± 1.7; 6-14</td>
<td>11 ± 4.9; 6-30</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Papillary muscle level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anteroseptal</td>
<td>10 ± 2.0; 7-17</td>
<td>22 ± 8.1; 9-40</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Lateral</td>
<td>9 ± 2.0; 6-17</td>
<td>12 ± 4.4; 7-30</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Posterior</td>
<td>9 ± 1.6; 6-12</td>
<td>11 ± 4.4; 6-30</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Inferior</td>
<td>9 ± 1.8; 6-15</td>
<td>12 ± 5.2; 6-30</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Parasternal long axis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anteroseptal</td>
<td>10 ± 1.8; 5-14</td>
<td>21 ± 7.7; 10-38</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Posterior</td>
<td>8 ± 1.8; 5-13</td>
<td>10 ± 4.1; 6-30</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Maximal wall thickness</td>
<td></td>
<td>24 ± 8; 11-40</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Values are mean value (mm) and SD; range.

Results

Echocardiographic characteristics of genetically affected subjects in this study are shown in Table 1. The ages of those studied ranged from 16 to 61 years (mean 33 ± 13) in the genetically affected group, compared with 19 to 70 years (mean 41 ± 13) in the unaffected group (p = 0.01). Twenty of the 39 affected subjects were women, as were 14 of the 30 unaffected subjects. A total of six mutations of the beta-myosin heavy-chain gene were represented in the families studied; all of these mutations cause a change in amino acid charge, with the exception of the Val 606- Met mutation, which does not result in a change in amino acid charge.

Wall thickness measurements. The mean wall thickness measurements at various locations and from various views are shown in Table 2. The mean maximal wall thickness at any location was 11 ± 2 mm in the unaffected cohort and 24 ± 8 mm in the affected cohort (Fig. 2) (p < 0.0001). The maximal wall thickness in the unaffected cohort was 17 mm, in a subject with a known history of hypertension. The maximal wall thickness in unaffected subjects without a history of hypertension was 13 mm. In the affected cohort, 1 patient had a maximal wall thickness < 12 mm, 4 patients had a maximal wall thickness between 12 and 15 mm, 9 had a maximal wall thickness between 15 and 20 mm and 25 had a maximal wall thickness >20 mm. The minimal wall thickness of any patient in the affected cohort was 11 mm. This patient was a 42-year old woman with a normal electrocardiogram who also had no evidence of systolic anterior mitral valve motion, right ventricular hypertrophy or abnormal ventricular morphology.

The mean septal/posterior wall ratio was 1.10 ± 0.2 in the unaffected group (range 0.67 to 1.77) compared with 1.75 ± 0.6 (range 0.86 to 3.6) in the affected cohort, as shown in Figure 3. Seventy-seven percent of patients in the affected group had a septal/posterior wall ratio ≥ 1.3 compared with 6% in the unaffected group. There was no significant association between age and extent of hypertrophy in either the affected or the unaffected cohort. The mean wall thickness variance at the mitral valve level for the unaffected cohort was 0.03 ± 0.03 (range 0.003 to 0.12) compared with 0.49 ± 0.48 (range 0.001 to 1.87) for the affected cohort (p < 0.0001). At the papillary muscle level, mean wall thickness variance was 0.02 ± 0.02 (range 0.0003 to 0.1) for the unaffected cohort compared with 0.44 ± 0.47 (range 0.001 to 1.87) for the affected cohort (p < 0.0001). Of nine affected patients with a septal/posterior wall ratio < 1.3, four had a wall thickness variance > 2 SD from the mean of the unaffected group, suggesting that this measure provides additional information beyond that of septal/posterior wall ratio. The most asymmetric ventricle in the unaffected cohort had a wall thickness variance of 0.12 (mean 0.03), whereas the mean wall thickness variance in the affected cohort was 0.49, indicating that ventricular asymmetry was much more extensive in the affected group.
Table 3. Qualitative Echocardiographic Features in 69 Subjects

<table>
<thead>
<tr>
<th>Status</th>
<th>Systolic Anterior Motion</th>
<th>Right Ventricular Hypertrophy</th>
<th>Ventricular Morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chordal Only (No.)</td>
<td>Hypertrophy With Normal Shape</td>
<td>Hypertrophy With Reversed Septal Curvature</td>
</tr>
<tr>
<td>Unaffected</td>
<td>30</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>%</td>
<td>100</td>
<td>93</td>
<td>100</td>
</tr>
<tr>
<td>Affected</td>
<td>15</td>
<td>29</td>
<td>17</td>
</tr>
<tr>
<td>%</td>
<td>38</td>
<td>74</td>
<td>44</td>
</tr>
</tbody>
</table>

Qualitative echocardiographic features. Table 3 demonstrates the qualitative echocardiographic features observed in unaffected and affected subjects. In the affected cohort, 76% had left ventricular hypertrophy primarily of the anterior septum, two patients (5%) had hypertrophy that was relatively equal in the anterior and posterior walls and one patient had hypertrophy primarily involving the right ventricle. Twenty-six percent of patients in the affected cohort had right ventricular hypertrophy, compared with 7% of subjects in the unaffected cohort (p < 0.04). Seventy-nine percent of patients in the affected cohort had the morphology of reversed septal curvature in the four-chamber apical view compared with none in the unaffected cohort (p < 0.0001).

Of affected patients with reversed septal curvature, five had a septal/posterior wall ratio <1.3, suggesting that this finding was not simply an artifact of ventricular asymmetry. Seventeen percent of patients in the affected cohort had qualitative evidence of left ventricular hypertrophy with normal ventricular morphology. No patients in either the affected or the unaffected cohort had ventricular hypertrophy that was confined to the proximal septum.

Systolic anterior motion of the mitral valve leaflets was present in 44% of affected patients, and 18% of affected patients had chordal systolic anterior motion only (p < 0.0001). None of the unaffected subjects had either chordal systolic anterior motion or systolic anterior motion involving the mitral valve leaflet. Two affected subjects with systolic anterior motion of the mitral valve had a maximal left ventricular wall thickness <15 mm, and three subjects with systolic anterior motion had a septal/posterior wall ratio <1.3.

In a univariate logistic regression analysis, maximal wall thickness, septal/posterior wall ratio and wall thickness variance were found to be significant predictors of affected status. Figures 4 and 5 demonstrate the probability of affected status at any given wall thickness or septal/free wall ratio, derived from a logistic regression using either maximal wall thickness or septal/posterior wall ratio as a continuous dependent variable. A patient genetically at risk for the disease with a wall thickness ≥16 mm or a septal/posterior wall ratio ≥1.5 had a ≥75% probability of being affected; a maximal wall thickness ≥18 mm or a septal/posterior wall ratio ≥1.87 was associated with a >95% probability of being affected. Of note, a septal/posterior wall ratio ≥1.3, which has previously been proposed as a diagnostic criterion (18), conferred a probability of 55% of being affected in this patient group.

To determine which variables present among affected and unaffected subjects were most predictive of genotype positivity, a backward stepwise multiple logistic regression analysis was performed, incorporating affected status as the dependent variable and maximal wall thickness, septal/posterior wall ratio, age, wall thickness variance and right ventricular hypertrophy as the independent variables. In this model, maximal wall thickness was the only variable that was independently predictive of genotype positivity (p < 0.02). Systolic anterior motion and abnormal ventricular morphology were seen only in patients with affected status and were therefore not included in this model.

Of the genetically affected subjects in this study, three had a maximal left ventricular wall thickness <15 mm,

Figure 4. Probability of affected status at any given maximal wall thickness derived from a univariate logistic regression model.
Asymmetric septal hypertrophy. Asymmetric septal hypertrophy has been considered a hallmark of this disease, with a septal/posterior wall ratio >1.3:1 regarded as diagnostic (22). In our study group, a septal/posterior wall ratio >1.3 had a sensitivity of 0.77, a specificity of 0.93, a positive predictive value of 0.94 and a negative predictive value of 0.76 for the diagnosis of affected status. Even in this highly enriched group, these indicators are not adequate for definitive diagnosis of the disorder. Because this is a group in which the a priori risk of having the disease is 50%, the echocardiographic diagnostic criteria used to assess whether an individual patient is affected must have a predictive value well above 50%. In our subjects, systolic anterior motion and reverse septal curvature had the best predictive values (100%), and a maximal wall thickness of 15 mm or a septal/posterior wall ratio of 1.5 was associated with a 75% probability of being affected. In an unselected group, these criteria are likely to be far less specific and less predictive.

Like septal/posterior wall ratio, the wall thickness variance quantifies the extent of ventricular asymmetry. The distribution of wall thickness variance in the normal cohort approached a perfectly symmetric score of zero, whereas the affected cohort had significantly greater asymmetry. Although the abnormal septal/posterior wall ratio in the affected cohort was probably a major contributor to asymmetry, wall thickness variance was independently predictive of genotype when controlling for septal/posterior wall ratio.

Systolic anterior motion. The presence of systolic anterior motion of the mitral valve usually correlates with the severity of outflow tract obstruction and is associated with septal hypertrophy (23). Previous studies have found that the diagnostic specificity of systolic anterior motion of the mitral valve for hypertrophic cardiomyopathy is 97% (24). In the present study, systolic anterior motion was characterized as either chordal or involving the mitral leaflets and did not further distinguish systolic anterior motion in which the anterior mitral valve leaflet apposed the septum. The percent of affected patients with leaflet systolic anterior motion in our study is similar to that previously described in patients with hypertrophic cardiomyopathy. Although Shapiro and McKenna (2) noted systolic anterior motion of the mitral valve in 47% of patients with hypertrophic cardiomyopathy, cause familial hypertrophic cardiomyopathy is inherited as an autosomal dominant trait with a penetrance that is >95% (7,11), persons who carry the gene would be expected to demonstrate some phenotypic evidence of the disease. This study confirms previous observations that although the majority of genetically affected persons demonstrate echocardiographic evidence of the disease, it is possible for affected adults who share a mutation with persons who are severely affected to have no echocardiographic evidence of disease (20). Whether these persons are at risk for arrhythmia or sudden death is currently unknown, although familial cases of sudden death have been reported (21) that have the characteristic histologic features of hypertrophic cardiomyopathy but no echocardiographic findings.

Discussion

By utilizing genotype as an independent diagnostic criterion for hypertrophic cardiomyopathy, this study describes the spectrum of two-dimensional echocardiographic abnormalities in the disease more completely than has been possible in studies that have relied on echocardiographic diagnosis to identify affected patients. The results of this study indicate that the range of abnormalities in familial hypertrophic cardiomyopathy is broad and that when applied to a population at risk for the disease, previously described diagnostic criteria may lack both sensitivity and specificity. This study confirms previous observations that there is significant heterogeneity of echocardiographic findings in hypertrophic cardiomyopathy and extends these observations to patients with missense mutations of the beta-myosin heavy chain gene.

Despite the myriad of abnormalities described in hypertrophic cardiomyopathy, many investigators have suggested that unexplained ventricular hypertrophy represents the primary morphologic abnormality of the disease (19). Because familial hypertrophic cardiomyopathy is inherited as an autosomal dominant trait with a penetrance that is >95% (7,11), persons who carry the gene would be expected to demonstrate some phenotypic evidence of the disease. This study confirms previous observations that although the majority of genetically affected persons demonstrate echocardiographic evidence of the disease, it is possible for affected adults who share a mutation with persons who are severely affected to have no echocardiographic evidence of disease (20). Whether these persons are at risk for arrhythmia or sudden death is currently unknown, although familial cases of sudden death have been reported (21) that have the characteristic histologic features of hypertrophic cardiomyopathy but no echocardiographic findings.

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other investigators (17,25) noted a greater prevalence of this finding, a difference that may reflect selection bias. In our study group, chordal systolic anterior motion was seen only in affected subjects, suggesting that inclusion of chordal systolic anterior motion in the definition of systolic anterior motion may increase its sensitivity as a diagnostic criterion.

Ventricular morphology. The left ventricular cavity in many patients with hypertrophic cardiomyopathy has been characterized as sigmoid, or “quarter-moon” in shape, with the septum bowing into the ventricular cavity (17). Lever et al. (17) used this criterion to distinguish hypertrophic cardiomyopathy in the elderly, a disease probably related to hypertension, from hypertrophic cardiomyopathy in the young. In their study group, only young patients with hypertrophic cardiomyopathy demonstrated reversed septal curvature, and a proximal septal bulge was seen only in elderly patients. Whereas seven of eight affected subjects with normal ventricular morphology in our cohort had hypertrophy, none of the affected in our cohort had hypertrophy isolated to the proximal septum. The sigmoid-shaped septum visualized in affected subjects in our study may reflect a pattern of hypertrophy in which the predominant hypertrophy occurs in the mid rather than the distal septum; nevertheless, this pattern is visually striking and may be useful in distinguishing hypertrophic cardiomyopathy from hypertrophy of other causes.

Study limitations. Because of the absence of Doppler evaluation in many patients, Doppler variables were not included in the analysis. Hemodynamic assessment of outflow gradients based on Doppler studies have added significantly to the understanding of hypertrophic cardiomyopathy. Nevertheless, outflow tract gradients can vary tremendously in individual patients over time and may not be present in a substantial number of patients considered to have hypertrophic cardiomyopathy. In addition, the relation between systolic anterior motion of the mitral valve and outflow tract obstruction in this patient group could not be addressed.

The data presented in this study do not address the sensitivity or specificity of these various diagnostic criteria in the population at large but reflect the findings of a specific, highly enriched population of persons who are genetically at risk for the disease. Clinicians are often faced with the practical problem of diagnosing hypertrophic cardiomyopathy in a family member of a known affected individual. The unaffected family members therefore serve as an appropriate and realistic control group even though they were not matched with the affected cohort. Our results are thus applicable to the adult population that is genetically at risk for the disease, although there is no reason to assume that the unaffected subjects analyzed in this study differ substantially from the normal population. Because echocardiograms were not available for a sufficient number of children in these families, this analysis was confined to family members over age 16 years. The results of this study should not be extrapolated to genetically affected or possibly affected children because they will be less likely to manifest clinical or echocardiographic findings of hypertrophic cardiomyopathy.

For the purposes of this analysis, members of 10 families were determined to be genotype positive if they demonstrated any of seven missense mutations of the beta-myosin heavy chain gene. Studies of other genetic diseases due to missense mutations, including cystic fibrosis, have demonstrated similar phenotypic characteristics from a variety of mutations of a single gene (26), although major phenotypic differences have been observed in patients with distinct mutations of the same gene. In this study, there were no overt differences in the echocardiographic characteristics seen in affected persons with distinct missense mutations. Although this study lacked adequate power to detect significant differences in echocardiographic characteristics associated with distinct missense mutations of the beta-myosin heavy chain gene (Table 1), the possibility that distinct missense mutations in the beta-myosin heavy chain gene are associated with differences in phenotypic expression remains.

Conclusions. In this study, there was no echocardiographic sine qua non for the diagnosis of hypertrophic cardiomyopathy, and no single echocardiographic finding was pathognomonic for the disease. The broad range of echocardiographic findings in the affected subjects included in this study should, for the clinician, raise the possibility that a patient may be genetically affected even without “classic” echocardiographic manifestations. Indeed, patients without echocardiographic evidence of the disease who are genetically affected may be at risk for arrhythmia or sudden death. The clinical characteristics of genetically affected persons who lack major phenotypic characteristics of the disease remain uncertain. Mutations in the beta-myosin heavy chain gene account for approximately half of the familial cases of hypertrophic cardiomyopathy (12,27,28), and our laboratory has recently demonstrated mutations in the beta-myosin heavy chain gene in nonfamilial cases (14). Although echocardiography will continue to play an important role in the diagnosis and management of patients with hypertrophic cardiomyopathy, genetic testing, when widely available, may supersede echocardiography as the test of choice for diagnosis in members of affected families.

References


