Diastolic abnormalities in patients with hypertrophic cardiomyopathy: relation to magnitude of left ventricular hypertrophy

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ABSTRACT To investigate the relationship between diastolic abnormalities and left ventricular hypertrophy, 52 patients with hypertrophic cardiomyopathy (HCM) and 22 normal subjects were studied with digitized M mode echocardiography and two-dimensional echocardiography. Echocardiographic indexes of diastolic function were compared in patients with different extent of left ventricular hypertrophy. Time interval from minimum left ventricular internal dimension to mitral valve opening and time to peak rate of increase in left ventricular internal dimension were significantly prolonged (80 ± 31 and 100 ± 37 msec, respectively) in patients with HCM and the most extensive left ventricular hypertrophy compared with those in patients with mild left ventricular hypertrophy (59 ± 25 and 74 ± 34 msec, respectively; p < .01). Furthermore, peak rate of posterior wall diastolic excursion was significantly reduced in those patients with HCM and posterior wall hypertrophy (8.3 ± 4.0 cm/sec) compared with that in patients with HCM but normal posterior wall thickness (11.2 ± 3.4 cm/sec; p < .002). However, abnormal M mode echocardiographic indexes of diastolic function were also identified in a substantial proportion of patients (i.e., 73%) with HCM and only mild left ventricular hypertrophy. In these patients, time interval from minimum left ventricular internal dimension to mitral valve opening (59 ± 25 msec), peak rate (12 ± 4 cm/sec), and time to peak rate of increase in left ventricular internal dimension (74 ± 34 msec) were significantly different from normal (25 ± 12 msec, 21 ± 3 cm/sec, and 49 ± 12 msec, respectively; p < .01). Furthermore, in 32 patients with HCM who had normal posterior wall thickness, peak rate of posterior wall diastolic excursion was significantly reduced (11.2 ± 3.4 cm/sec) compared with normal (16.7 ± 2.4 cm/sec; p < .001). In conclusion, our findings show a relationship, in patients with HCM, between magnitude of left ventricular hypertrophy and extent of diastolic wall motion abnormalities. However, our results also show that diastolic wall motion abnormalities are common in patients with HCM and mild localized left ventricular hypertrophy and may even be identified in segments of the left ventricle that are of normal thickness. These data suggest that the primary cardiomyopathic process in HCM may not be limited to areas of gross wall thickening, and nonhypertrophied regions of the left ventricle may contribute to impairment of diastolic function in patients with this disease.


HYPERTROPHIC CARDIOMYOPATHY (HCM) is characterized by both increased ventricular wall thickness1 6 and impairment of left ventricular filling.7–11 However, the interrelation between these two pathologic features of the disease is not well understood. For example, it is not known whether left ventricular dia-

stolic dysfunction is solely the consequence of hypertrophy, or if diastolic abnormalities may also be present in ventricles with only mild left ventricular hypertrophy. The purpose of the present investigation was to define the relationship, in patients with HCM, between the magnitude of left ventricular hypertrophy (LVH) as assessed with M mode and two-dimensional echocardiography and the impairment in left ventricular diastolic wall motion evaluated with digitized M mode echocardiography.

Methods

Selection and characterization of patients. Fifty-two patients with HCM comprise the study population: 30 were evalu-
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ated at the National Heart, Lung, and Blood Institute, and 22 were evaluated at the Ente Ospedaliero Ospedali Galliera. The diagnosis of HCM was established by typical clinical findings, and by two-dimensional echocardiographic demonstration of localized or diffuse hypertrophy in a nondilated left ventricle, in absence of another cardiac or systemic disease that could produce LVH. Patients were selected for this study on the basis of the following criteria: (1) a high-quality M mode echocardiogram, with optimal visualization of the ventricular septum and the left ventricular posterior wall sufficient to allow clear identification of the borders of these structures, and (2) a technically satisfactory two-dimensional echocardiogram, with clear recognition of the endocardial and epicardial borders of the left ventricular wall in the parasternal short-axis and long-axis views permitting reliable identification of the distribution and extent of LVH.

The 52 study patients with HCM ranged in age from 9 to 70 years (mean 37; 39 (75%) were male patients. Thirty-two patients were asymptomatic. 13 had mild functional limitation (New York Heart Association functional class II), and seven had moderate functional limitation (class III). Echocardiographic studies were performed at least 48 hr after cessation of all cardiac medications; all patients were in normal sinus rhythm.

Magnitude of left ventricular outflow tract obstruction under basal conditions was assessed at cardiac catheterization in 12 patients and estimated from the M mode echocardiogram based on the magnitude and duration of systolic anterior motion of the mitral valve in the other 40. Left ventricular outflow tract obstruction under basal conditions (gradient ≳ 30 mm Hg) was considered to be present in 10 patients and was absent or less than 30 mm Hg in the other 42.

Twenty-two normal volunteers without evidence of cardiovascular disease served as control subjects. They ranged in age from 15 to 55 years (mean 30); 15 (64%) were male subjects.

Echocardiography. An Advanced Technology Laboratory (ATL) Mark 300 or Mark 500 mechanical sector scanner with a 3 MHz transducer was used to perform the echocardiographic studies. M mode echocardiographic recordings were made while the cardiac anatomy was visualized with two-dimensional echocardiography. The M mode echocardiographic cursor was positioned at the level of the mitral valve, where the ventricular septum, the left ventricular posterior wall, and the point of separation of the mitral leaflets were best imaged. Because the diastolic slope of the left ventricular posterior wall may vary considerably depending on the angulation of the M mode beam, care was taken to obtain the echocardiographic recordings with the beam perpendicular to the posterior wall where the maximum diastolic slope of the posterior wall was visualized. Thickness of ventricular septum and left ventricular posterior wall was measured at mitral valve level, according to the criteria of the American Society of Echocardiography. M mode echocardiograms were recorded at a paper speed of 100 mm/sec.

The two-dimensional echocardiographic examination, performed to identify the extent and distribution of LVH, included the imaging of a number of cross-sectional planes through the heart. Serial short-axis views of the left ventricle were obtained by maintaining the transducer in a fixed location on the chest wall and slowly angling the image plane from aorta to apex. The long-axis view was obtained by orienting the sector plane at a 90 degree angle to the short-axis plane and parallel to the longitudinal axis of the left ventricle. The apical four-chamber view was obtained with the transducer positioned at the left ventricular apex, and the image plane was directed perpendicular to the ventricular and atrial septa. Finally, the transducer was rotated clockwise from the apical four-chamber view so that the ultrasound beam was approximately parallel to the ventricular septum, permitting simultaneous visualization of the aorta and left ventricular outflow tract. Two-dimensional echocardiographic images were recorded on 1 inch reel-to-reel Sony videotape or on Panasonic NV-8200 videotape.

Digitized M mode echocardiography. Measurement of indexes of diastolic function were obtained with digitized M mode echocardiography. In each patient, two to five (an average of four) consecutive cardiac cycles with clearly identifiable left septal and posterior wall endocardial echoes were digitized and the values were averaged. Contours of the left side of the septum and the endocardium of the posterior wall were traced, and the point of initial opening of the mitral valve was identified. Digitization was performed with a hand-controlled cursor (Hewlett-Packard Graphic Tablette 9111A) and processed by a Hewlett-Packard 1000 computer system that provided a continuous plot of change in left ventricular internal dimension, its first derivative, and the first derivative of the posterior wall endocardial excursion.

The following echocardiographic parameters of diastolic function were derived from this computer analysis: time interval from minimum left ventricular internal dimension to mitral valve opening, peak rate of increase in left ventricular internal dimension, time to peak rate of increase in left ventricular internal dimension (measured as the time interval from minimum left ventricular internal dimension to maximal rate of increase in left ventricular internal dimension), and peak rate of posterior wall diastolic excursion.

Assessment of LVH

Overall extent and distribution of LVH. The pattern of LVH was assessed in a semiquantitative fashion from the two-dimensional echocardiogram. This analysis primarily utilized the parasternal short-axis planes. However, the parasternal long-axis view was also useful in evaluating the extent of LVH in the anterior ventricular septum, and the apical views were used primarily to exclude the presence of hypertrophy in the apical portion of the left ventricle.

The location and extent of LVH was defined with respect to the short-axis cross-sectional plane (figure 1). The ventricular septum was divided into two approximately equal segments (anterior and posterior); the left ventricular free wall was divided into lateral and posterior segments. Hypertrophy of the anterior ventricular septum and the posterior free wall was considered to be present if the wall was at least 15 mm in thickness. The posterior portion of septum and lateral free wall are visual-

FIGURE 1. Segments of left ventricular wall visualized by two-dimensional echocardiography in the short-axis view. The points of insertion of the right ventricle into the left ventricle are the anatomic landmarks dividing the ventricular septum (VS) from the left ventricular free wall. A = anterior; L = left; P = posterior; R = right.
TABLE 1
Clinical data and digitized parameters of diastolic function in control subjects and in three subgroups of patients with HCM and different magnitudes of LVH

<table>
<thead>
<tr>
<th></th>
<th>Age (yr)</th>
<th>Sex (% male)</th>
<th>Heart rate (beats/min)</th>
<th>VS thickness (\delta) (mm)</th>
<th>PW thickness (\delta) (mm)</th>
<th>Symp-toms (% patients)</th>
<th>dD/dt (cm/sec)</th>
<th>T max (msec)</th>
<th>T to MVO (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td>30</td>
<td>64</td>
<td>75 ± 15</td>
<td>9 ± 2(^a)</td>
<td>8 ± 2</td>
<td>1.1</td>
<td>0</td>
<td>21 ± 3(^b)</td>
<td>49 ± 12(^b)</td>
</tr>
<tr>
<td>(n = 22)</td>
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<td></td>
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<tr>
<td>HCM</td>
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<tr>
<td>Mild LVH</td>
<td>40</td>
<td>87</td>
<td>68 ± 12</td>
<td>16 ± 4</td>
<td>11 ± 3</td>
<td>1.5</td>
<td>33</td>
<td>12 ± 4</td>
<td>74 ± 34</td>
</tr>
<tr>
<td>(n = 15)</td>
<td>(9–70)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate LVH</td>
<td>31</td>
<td>60</td>
<td>67 ± 11</td>
<td>20 ± 8</td>
<td>11 ± 2</td>
<td>1.8</td>
<td>30</td>
<td>12 ± 4</td>
<td>108 ± 33(^c)</td>
</tr>
<tr>
<td>(n = 10)</td>
<td>(13–45)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe LVH</td>
<td>37</td>
<td>74</td>
<td>72 ± 14</td>
<td>25 ± 8(^d)</td>
<td>12 ± 3</td>
<td>2.3</td>
<td>44</td>
<td>11 ± 4</td>
<td>100 ± 37(^d)</td>
</tr>
<tr>
<td>(n = 27)</td>
<td>(9–67)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

\(dD/dt = \text{peak rate of increase in left ventricular internal dimension; PW = posterior wall; T to MVO = time from minimum left ventricular internal dimension to mitral valve opening; T max dD/dt = time to peak rate of increase in left ventricular internal dimension; VS = ventricular septum; VS/PW = ratio of ventricular septal to posterior wall thickness.}\)

\(^a\) Obtained by M mode echocardiography at mitral valve level, according to the criteria of the American Society of Echocardiography. \(^b\)

\(^c\) For each of these parameters, values for normal subjects were significantly different from each of the subgroups of patients with HCM (p < .005).

\(^d\) Each of these parameters was significantly different when compared to the subgroup of patients with HCM and mild LVH (p < .01).

\(^e\) This parameter was significantly different when compared to the subgroup of patients with HCM and moderate LVH (p < .02).

ized in the lateral regions of the sector (in the short-axis plane) where resolution is less than optimal. Therefore, to ensure that the frequency with which hypertrophy in these segments was identified would not be overestimated, the posterior septum and lateral free wall were considered hypertrophied only if the wall was judged to be at least 17 mm in thickness. \(^6\) Wall thickness was assessed directly from the television monitor with the aid of calipers and with the use of a calibration scale produced by the instrument. Location of endocardial and epicardial borders was identified by viewing the pertinent portions of videotape in slow-motion and real-time modes. In some instances, wall thickness was also measured in the stop-action mode at end-diastole from the television monitor.

On the basis of these two-dimensional echocardiographic criteria, the number of hypertrophied left ventricular segments was identified and the study patients were divided into three subgroups with regard to overall extent of LVH as follows: mild LVH, involving only one left ventricular segment (15 patients); moderate LVH, involving two segments (10 patients); severe LVH, involving three or four segments (27 patients). Patients with HCM and different magnitudes of LVH and control subjects were similar with respect to age, sex, and heart rate (table 1).

Posterior wall hypertrophy: In patients with HCM, the portion of left ventricular posterior wall identified by M mode echocardiography may be of normal or increased thickness. \(^6\) Therefore, we considered this region of the left ventricular wall of particular interest in the present investigation, because it offered the opportunity to assess diastolic motion of the left ventricular wall in the presence or in the absence of hypertrophy.

The 52 study patients with HCM were divided into two groups on the basis of left ventricular posterior wall thickness. M mode echocardiography was used to assess posterior wall thickness because the M mode beam visualizes this region with greater ultrasound resolution than does two-dimensional echocardiography. The posterior wall was normal (≤11 mm) \(^22,\ 23\) in 32 patients, and hypertrophied (>11 mm) in the remaining 20 patients. Patients with HCM (with or without posterior wall thickening) did not differ from the control subjects with respect to age, sex, or heart rate (table 2).

Reproducibility of the study measurements. Intraobserver and interobserver reproducibility of the digitized echocardiographic measurements was assessed in 31 study patients (14 with HCM and 17 controls). To assess intraobserver variability, one investigator digitized two different sets of four cardiac cycles in each patient. Values from the four cardiac cycles were averaged. To assess interobserver variability, two investigators digitized two different sets of four cardiac cycles in each patient. Values from the four cardiac cycles were averaged. The coefficients of variation for these digitized measurements were obtained for each of the 31 patients and the intraobserver and interobserver mean coefficients of variation were calculated. \(^24\) Values for intraobserver and interobserver reproducibility (expressed as mean coefficient of variation) were, respectively, 8.8% and 10.7% for time interval from minimum left ventricular internal dimension to mitral valve opening, 5.6% and 5.1% for peak rate of increase in left ventricular internal dimension.

TABLE 2
Clinical data in control subjects and in patients with HCM and either normal or increased posterior wall thickness

<table>
<thead>
<tr>
<th></th>
<th>Age (yr)</th>
<th>Sex (% male)</th>
<th>Heart rate (beats/min)</th>
<th>PW thickness (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td>30</td>
<td>64</td>
<td>75 ± 15</td>
<td>8 ± 2</td>
</tr>
<tr>
<td>(n = 22)</td>
<td>(15–55)</td>
<td></td>
<td></td>
<td>(6–11)</td>
</tr>
<tr>
<td>HCM with PW ≤11 mm</td>
<td>34</td>
<td>78</td>
<td>68 ± 13</td>
<td>10 ± 1</td>
</tr>
<tr>
<td>(n = 32)</td>
<td>(9–67)</td>
<td></td>
<td></td>
<td>(6–11)</td>
</tr>
<tr>
<td>HCM with PW &gt;11 mm</td>
<td>41</td>
<td>70</td>
<td>72 ± 13</td>
<td>14 ± 2</td>
</tr>
<tr>
<td>(n = 20)</td>
<td>(15–70)</td>
<td></td>
<td></td>
<td>(12–18)</td>
</tr>
</tbody>
</table>

\(PW = \text{posterior wall.}\)
15.0% and 12.1% for time to peak rate of increase in left ventricular internal dimension, and 6.8% and 5.3% for peak rate of posterior wall diastolic excursion.

Intraobserver agreement on the determination of overall extent of LVH, as assessed from two-dimensional echocardiography, was evaluated in the first 16 patients with HCM who entered the study. Two interpretations of the same echocardiographic study, obtained by one observer 5 months apart, were compared. There was complete agreement regarding the number of hypertrophied segments in 14 of the 16 patients (88%).

Statistical methods. Data were expressed as mean ± SD. Differences between means were determined by the one-way analysis of variance. Differences between proportions were determined with the chi-square test.

Results

Relationship between overall extent and distribution of LVH and digitized echocardiographic indexes of diastolic function. Patients with HCM were classified according to the distribution and extent of LVH and then compared with respect to the echocardiographic indexes of diastolic function. Time interval from minimum left ventricular internal dimension to mitral valve opening and peak rate and time to peak rate of increase in left ventricular internal dimension were significantly different in each of the three morphologic subgroups of patients with HCM when compared with normal (table 1). When echocardiographic parameters of diastolic function were analyzed with regard to individual patients, 45 (87%) of the 52 patients with HCM showed diastolic impairment, defined as the coexistence of at least two abnormal echocardiographic parameters of diastolic function. Both the time interval from minimum left ventricular internal dimension to mitral valve opening and peak rate of increase in left ventricular internal dimension were prolonged in patients with severe LVH (80 ± 31 and 100 ± 37 msec), compared with those in patients with mild LVH (59 ± 25 and 74 ± 34 msec, respectively; p < .01) (figures 2 and 3). In patients with moderate LVH, time interval from minimum left ventricular internal dimension to mitral valve opening and peak rate of increase in left ventricular internal dimension were intermediate and not significantly different from those in the other two groups; time to peak rate of increase in left ventricular internal dimension was significantly prolonged in patients with moderate LVH (108 ± 33 msec) compared with that in patients with mild LVH (74 ± 34 msec; p < .01).

Of note, echocardiographic diastolic abnormalities were common in patients with mild LVH. Values for peak rate of increase in left ventricular internal dimension were below the lower limit of normal in 12 (80%) of the patients with mild LVH; time to peak rate of increase in left ventricular dimension and time from minimum left ventricular dimension to mitral valve opening also exceeded the upper limit of normal in seven (47%) and nine (60%) of the patients, respectively. In these patients with mild LVH, each of these three parameters was significantly different from normal (table 1).

Relationship between posterior wall thickness and posterior wall diastolic dynamics. Peak rate of diastolic posterior wall excursion was significantly reduced in the 20 patients with HCM and increased left ventricular posterior wall thickness (8.3 ± 4.0 cm/sec) compared with that in the 32 patients with HCM but normal left ventricular posterior wall thickness (11.2 ± 3.4 cm/sec; p < .002) (figure 4). Peak rate of posterior wall diastolic excursion was also significantly reduced in the 32 patients with HCM and normal posterior wall thickness (11.2 ± 3.4 cm/sec) compared with that in control subjects (16.7 ± 2.4 cm/sec; p < .001) (figures 4 and 5), and in 19 (59%) of these 32 patients it was below the lower limit measured in the control subjects.

Discussion

Previous studies have demonstrated that diastolic function is impaired in most patients with HCM.9-14 Prolonged isovolumetric relaxation9,12 and diminished rapid diastolic filling7-14 have been identified with digitized echocardiography, radionuclide angiography, and with measurements obtained at cardiac catheterization. Diastolic impairment, as assessed with digi-
tized M mode echocardiography, was detected in over 80% of our study patients with HCM.

Unlike previous studies, 7-14 in the present investigation of patients with HCM we analyzed the relationship between the magnitude of LVH and the severity of diastolic abnormalities. Both the time interval from minimum left ventricular internal dimension to mitral valve opening and the time to peak rate of increase in left ventricular internal dimension were significantly prolonged in patients with the most extensive LVH compared with those in patients with mild LVH. Furthermore, peak rate of diastolic posterior wall excursion was significantly reduced in patients with posterior wall hypertrophy compared with that in patients with HCM but normal posterior wall thickness. Hence, our findings suggest that more severe diastolic abnormalities, as detected with digitized M mode echocardiography, are present in patients with the most extensive hypertrophy of the left ventricle.

On the other hand, we also identified diastolic abnormalities in patients with HCM and only mild LVH, i.e., with LVH limited to no more than one left ventricular segment. For example, in patients with mild LVH, time from minimum left ventricular internal dimension to mitral valve opening, as well as peak rate and time to peak rate of increase in left ventricular internal dimension, were significantly different from normal, and at least two of these indexes were impaired in more than 70% of these patients. Furthermore, diastolic wall motion abnormalities were frequently identified in nonhypertrophied segments of the left ventricle of patients with HCM. For example, peak rate of posterior wall diastolic excursion was significantly reduced in patients with normal posterior wall thickness compared with that in control subjects, and the values for this parameter fell below the lower limit of normal in about 60% of these patients.

These findings raise certain conceptual issues regarding the relationship between hypertrophy and the cardiomyopathic process in HCM. Most investigators agree that the thickened, noncompliant left ventricle constitutes the primary morphologic and functional expression of the cardiomyopathic process in the majority of patients with HCM. 4, 7-14 However, while our data show an association between marked hypertrophy and impaired left ventricular diastolic wall motion, we also found that diastolic abnormalities were common in left ventricles with only mild hypertrophy and were also present in nonhypertrophied left ventricular seg-

![Fig 3](image1.png)

**FIGURE 3.** Comparison of time to peak rate of increase in left ventricular (LV) internal dimension in normal subjects and in patients with HCM having mild, moderate, or severe LVH.

![Fig 4](image2.png)

**FIGURE 4.** Comparison of peak rate of posterior wall diastolic excursion in normal subjects, in patients with HCM and normal (≤11 mm) posterior wall thickness, and in patients with HCM and increased (>11 mm) posterior wall thickness. PW = posterior wall.
ments. These findings suggest that gross wall thickening may not be the sine qua non of impaired diastolic function in patients with HCM. Although the observations reported here do not provide an explanation for the mechanism of abnormal diastolic wall motion in nonhypertrophied segments of the left ventricle, previous necropsy studies have shown myocardial fibrosis and intramural coronary artery abnormalities to be common in patients with HCM. It is possible that such structural alterations may be partially responsible for diastolic abnormalities in nonhypertrophied (as well as hypertrophied) segments of the left ventricle.

In the present study, we used digitized echocardiography, in a manner similar to other investigators, to assess left ventricular diastolic dynamics. We acknowledge that the indexes of diastolic function measured with this technique are not solely influenced by left ventricular wall thickness and by the intrinsic properties of the left ventricular wall, but are also dependent on the loading conditions of the ventricle. Therefore, changes in left atrial driving pressure or in residual left ventricular volume from the preceding systole may alter these diastolic indexes independent of left ventricular wall thickness. In addition, cardiac motion (relative to the fixed position of the echo transducer on the chest) may influence echocardiographic measurements of wall motion such as the excursion of the posterior wall endocardium. Because hemodynamic measurements were not obtained in the present investigation, the influence of wall thickness on diastolic wall motion could not be separated, in the individual patient, from the potential influence of loading conditions. However, our observations that diastolic wall motion abnormalities were more severe in patients with diffuse LVH, and were also common in patients with mild localized LVH, were based on analysis of group data. While in individual patients such diastolic abnormalities could conceivably be explained as the consequence of variables other than wall thickness, this interpretation is unlikely for our patient subgroups that were segregated exclusively on the basis of the magnitude of LVH.

In conclusion, our data show a relationship, in patients with HCM, between magnitude of LVH and severity of diastolic wall motion abnormalities. Our results also show that diastolic wall motion abnormalities may be identified in patients with HCM and mild LVH (i.e., hypertrophy involving only one segment of the left ventricle) and that impaired diastolic wall motion may also be present in nonhypertrophied left ventricular segments. The pathogenesis of diastolic wall motion abnormalities in patients with HCM and mild localized LVH remains to be determined.

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References


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