Development and Determinants of Dynamic Obstruction to Left Ventricular Outflow in Young Patients With Hypertrophic Cardiomyopathy

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Background. To study the development of dynamic subaortic obstruction in young patients with hypertrophic cardiomyopathy (HCM), serial echocardiograms were retrospectively analyzed in a group of 26 consecutive children with this disease who showed no evidence of dynamic outflow obstruction at their initial evaluation (age, 11±3 years).

Methods and Results. After a follow-up of 3–12 years (mean, 7±3 years), seven of the 26 patients (27%) developed echocardiographic evidence of subaortic obstruction, i.e., marked systolic anterior motion (SAM) of the mitral valve with mitral–septal apposition and increased left ventricular outflow tract systolic velocities (3.8±0.3 m/sec; range, 3.1–4.5). Patients who developed SAM had smaller transverse dimension of the left ventricular outflow tract and more anteriorly displaced mitral valve when initially evaluated than did patients without development of SAM (outflow tract dimension, 19.1±4 versus 24.6±4 mm; mitral valve position index, 1.07±0.2 versus 0.73±0.3; each p<0.02). In patients with development of SAM, the already reduced outflow tract dimension decreased further during follow-up, and the mitral valve became even more anteriorly displaced within the left ventricular cavity. These developmental alterations in outflow tract size were associated with increases in left ventricular wall thickness, particularly of the basal anterior septum (11.0±4 versus 12.6±4 mm; p<0.02). In patients with development of SAM, the mitral valve apposition and the mitral valve position index were not different from those observed in patients without SAM at the time of initial evaluation (age, 6±3 years).

Conclusions. Development of subaortic obstruction in young patients with HCM results from a process of dynamic remodeling of left ventricular geometry over several years and is characterized by progressive narrowing of the outflow tract with anterior displacement of the mitral valve and disproportionate thickening of the basal anterior ventricular septum. (Circulation 1992;85:1398–1405)

Key Words • hypertrophic cardiomyopathy • mitral valve • echocardiography

Hypertrophic cardiomyopathy (HCM) is a genetically transmitted primary cardiac disease characterized by a hypertrophied nondilated left ventricle that exhibits a wide spectrum of clinical, morphological, and hemodynamic features. Obstruction to left ventricular outflow occurs in an important minority of patients with HCM; it usually results from midsystolic apposition between mitral valve and anterior ventricular septum and may be responsible for symptoms and clinical deterioration.

Although much attention has been focused on the pathophysiology, clinical implications, and treatment of left ventricular outflow obstruction in patients with HCM, the timing and morphological determinants of its development are not known. Previous studies of infants with HCM have shown that subaortic obstruction may be present at or shortly after birth, suggesting that outflow obstruction can develop in utero. However, the striking and dynamic increases in left ventricular wall thickness previously identified by serial two-dimensional echocardiography in children with HCM14–15 suggested to us the hypotheses that 1) subaortic obstruction might also develop during this period of rapid growth and important modifications in left ventricular structure and geometry, and 2) specific morphological changes that can be identified by echocardiography might be associated with (and are probably causally related to) the development of outflow obstruction. Therefore, the present investigation was undertaken to determine whether dynamic subaortic obstruction can develop de novo in young patients with HCM and to define the morphological changes that characterize and may contribute causally to the occurrence of this phenomenon.

Methods

Selection of Patients

The case records of the Cardiology Branch of the National Heart, Lung, and Blood Institute from 1979 to 1989 were reviewed. During this period, 107 patients with HCM ≤15 years of age were evaluated. Of these 107, 63 patients were excluded because the initial echocardiographic evaluation already showed moderate to severe systolic anterior motion (SAM) of the mitral...
valve (grades 2–4+, as defined below). Therefore, 44 patients showed no evidence of dynamic subaortic obstruction under basal conditions on their initial echocardiographic examination, i.e., no or only mild SAM (grades 0 or 1+, as defined below). Of these 44 patients, three were excluded because they demonstrated intermediate degrees of SAM (grade 2+, as defined below) at the most recent evaluation. This judgment was based on the fact that patients with moderate SAM do not have resting subaortic obstruction but may show important intraventricular gradients with provocative maneuvers, thus creating ambiguity in ascertaining whether subaortic obstruction had developed in these three patients. In addition, 14 other patients were excluded because echocardiographic follow-up was less than 3 years, and one other was excluded because the echocardiographic studies were of suboptimal technical quality. Thus, the remaining 26 patients with HCM constitute the present study group by virtue of being ≤15 years old without echocardiographic evidence of outflow obstruction at initial evaluation and having subsequent echocardiographic evaluations over at least a 3-year period that allowed unequivocal assessment of the development of SAM and subaortic obstruction. Diagnosis of HCM was based on the demonstration of a hypertrophied, nondilated left ventricle in the absence of another cardiac or systemic disease that could produce cardiac hypertrophy. Patients were 5–15 years old (mean, 11±3 years) at initial evaluation and 8–25 years (mean, 18±4 years) at the most recent evaluation; follow-up was 3–12 years (mean, 7±3 years). Of the 26 patients, 23 were male and three were female.

Echocardiography

Two-dimensional. Echocardiographic examinations were performed using commercially available instruments. Two-dimensional echocardiograms were sequentially recorded on 3/4-in. format videotapes to allow serial review and rapid comparison of studies. Images were obtained in a number of cross-sectional planes using standard transducer positions.

In the short-axis plane, the left ventricle was divided into four segments that comprised the anterior and posterior ventricular septum and anterolateral and posterior left ventricular free wall. Presence and extent of left ventricular hypertrophy in these four left ventricular regions were evaluated in diastole directly from the video monitor with the aid of calipers. Wall thickness was measured at the levels of both the mitral valve and the papillary muscles. The magnitude and distribution of left ventricular hypertrophy was assessed primarily in the parasternal short-axis plane, although parasternal long-axis and apical views were also used to integrate the information obtained from the short-axis images. Previous studies from our laboratory using identical methodology have shown satisfactory reproducibility for measurements of left ventricular wall thickness.

A wall thickness index was also used to assess the magnitude of left ventricular hypertrophy. This index was calculated by adding measurements of the maximum wall thickness obtained in each of the four left ventricular segments. This calculated score has been used as a quantitative expression of the overall magnitude of left ventricular hypertrophy in patients with HCM.

For the anterior ventricular septum, maximum wall thicknesses were assessed at both its basal (region extending from cardiac base to the inferior margins of the anterior mitral leaflet) and distal (region caudal to the mitral leaflets) segments. For other regions of left ventricle, the portion with the greatest thickness (whether situated at the basal or distal level) was reported as the maximal thickness of that segment.

In each patient, changes in wall thickness were assessed by comparing the same left ventricular segment in the initial and most recent echocardiogram. Wall thickness was considered to have changed when maximal thickness of the same segment showed a difference of ≥5 mm between the two studies.

M-mode. M-mode echocardiograms were derived from the two-dimensional image under direct anatomic visualization. Cardiac dimensions were assessed according to the criteria of the American Society of Echocardiography. Mitral valve position index was calculated at the onset of systole by dividing the distance between mitral valve and posterior left ventricle free wall endocardium by the distance between the mitral valve and ventricular septal endocardium. Transverse left ventricular outflow tract dimension was measured as the distance between the mitral valve and the ventricular septal endocardium at the onset of systole (point of mitral valve closure) (see Figure 1A). Previous studies have demonstrated satisfactory reproducibility for measurements of left ventricular outflow tract dimension, for which the mitral valve position index is a derivative.

Assessment of dynamic subaortic obstruction. Because the study patients were asymptomatic (or only mildly symptomatic) throughout follow-up, outflow tract gradient was not measured by cardiac catheterization as part of their clinical evaluation. Obstruction to left ventricular outflow at the initial evaluation and on subsequent serial echocardiographic examinations was assessed from M-mode echocardiogram by analysis of the presence and extent of SAM of the mitral valve and graded as follows: 0, absent; 1+, present with the minimum distance between mitral valve and ventricular septum during systole >10 mm; 2+, without mitral–septal contact but with a distance of <10 mm between mitral valve and septum during systole; 3+, brief mitral–septal contact (<30% of the time between closure and opening of the mitral valve); 4+, prolonged apposition of mitral valve with septum (>30% of the time between closure and opening of the mitral valve). Patients with no or only mild SAM (i.e., 0 or 1+) at their initial evaluation were judged to be nonobstructive. Subaortic obstruction was considered to have developed when the most recent echocardiographic examination demonstrated a marked degree of SAM with mitral–septal contact (i.e., grades 3+ and 4+).

At the most recent evaluation, continuous-wave Doppler examination was also used to quantitatively estimate the magnitude of subaortic gradient. Doppler examinations were obtained using a 1.9-MHz nonimaging transducer. Studies were performed from the apical window with the patient in the supine or left lateral decubitus position during quiet respiration. Particular care was taken to separate the outflow tract signal from that of
mitral regurgitation. After the peak systolic velocity across the left ventricular outflow tract was determined, the pressure gradient was estimated with the modified Bernoulli equation**: $G = 4V^2$, where $G$ is the gradient (in mm Hg), and $V$ is the maximum flow velocity (in m/sec).

Data Analyses

All 161 echocardiograms obtained during follow-up in the 26 study patients were reviewed to aid in the assessment of the development of SAM and serial morphological changes and specifically to analyze the temporal relation between these changes and the development of SAM and subaortic obstruction. In each patient, the measurements derived from the echocardiograms obtained at intermediate points in time between the initial and most recent studies were consistent with gradual morphological changes in transition between those observed at the initial and most recent evaluations. In the interest of clarity and simplicity of presentation, only the data obtained at the initial and most recent evaluations were subjected to statistical analysis.

Differences between means were assessed with a paired or unpaired Student’s t test or one-way analysis of variance when appropriate. Differences between proportions were analyzed using the $\chi^2$ test. A probability value of less than 0.05 was considered to be statistically significant.

Results

Changes in Mitral Systolic Anterior Motion

During the follow-up period, seven of the 26 study patients (27%) developed marked SAM with mitral-septal contact (brief in four and prolonged in three), and therefore were considered to have developed subaortic obstruction (Figure 1). Also, at the most recent evaluation, continuous-wave Doppler examination performed in six of these seven patients confirmed the presence of subaortic obstruction by showing increased peak outflow tract velocity ranging from 3.1 to 4.5 m/second (estimated peak instantaneous outflow gradient, 38–81 mm Hg) (Figure 1).

The other 19 study patients (73%) did not show SAM at any time during follow-up. Continuous-wave Doppler examination performed in 17 of these patients at the most recent evaluation showed normal left ventricular outflow tract velocities in each case (<1.8 m/sec; mean, 1.5±0.3 m/sec). These 19 patients without development of subaortic obstruction during follow-up served as a control group for the purpose of morphological comparisons.

Progression of Left Ventricular Hypertrophy

At the initial evaluation, patients who either did or did not subsequently develop SAM showed no significant differences with respect to magnitude and distribution of left ventricular hypertrophy (Table 1). However, over the follow-up period, 23 of the 26 study patients (seven with and 16 without development of SAM) showed marked progression of left ventricular hypertrophy with an increase in left ventricular wall thickness of ≥5 mm; this increase in wall thickness significantly exceeded that expected to occur concomitantly with normal body growth.

During follow-up, the seven patients who developed SAM showed a greater increase in basal anterior ventricular septal thickness (from 18.7±7 to 29.7±7 mm; percent change, 72±33%) than did the 19 control patients who did not develop SAM (from 13.5±5 to 16.7±4 mm; percent change, 17±10%; $p<0.05$) (Figure 2). However, no differences were observed between the two groups regarding increase in thickness of any other left ventricular segment (or the overall magnitude of hypertrophy as expressed by the mass index) during follow-up (Figure 2). As a consequence of this dissimilar progression in left ventricular hypertrophy between the two groups, the basal anterior septum was significantly thicker at the most recent evaluation in patients with than in patients without development of SAM, but no differences were observed in the ultimate thicknesses of the other left ventricular segments (Table 1 and Figure 3).

In four of the seven patients who developed SAM, serial echocardiographic examinations were performed at approximately annual intervals over 5–11 years, thereby permitting assessment of the temporal relation between increasing left ventricular wall thickness and the development of SAM (and dynamic subaortic obstruction). In these four patients, SAM with mitral-septal apposition was initially identified with echocardiography at age 15 years (one patient), at 16 years (two patients), and at 19 years (one patient). In each, the predominant increase in basal anterior septal thickness occurred before the development of subaortic obstruction (15.6±4 mm; range, 12–21 mm), whereas the increase in thickness that occurred thereafter was relatively mild (2.5±3 mm; range, 0–6 mm; $p<0.001$).

Changes in Outflow Tract Dimension

At initial evaluation, transverse dimension of the left ventricular outflow tract was significantly smaller in those patients who subsequently developed SAM (19.1±4 mm) than in control patients without SAM (24.6±4 mm; $p<0.02$) (Figure 4). Also, the two groups differed significantly regarding the observed change in left ventricular outflow tract size during follow-up. Patients who developed SAM demonstrated a small decrease in outflow tract dimension, whereas patients without SAM showed a small increase in this dimension (change in outflow tract dimension, −3.3±5 versus 2.0±3 mm, respectively; $p<0.005$). Consequently, at the most recent evaluation, left ventricular outflow tract size was substantially less in the patients with SAM (15.8±2 mm) than in controls without SAM (26.2±3 mm; $p<0.0001$) (Figure 4).

Changes in Mitral Valve Position

At initial evaluation, the mitral valve was positioned more anteriorly within the left ventricular cavity in those patients who subsequently developed SAM (mitral valve position index, 1.07±0.2) than in patients without SAM (index, 0.73±0.3; $p<0.02$) (Figure 5). Over the period of follow-up, the mitral valve became even more anteriorly displaced in patients who developed SAM (change in mitral valve position index, 0.49±0.4 versus 0.04±0.2; $p<0.05$). Therefore, at the most recent evaluation, the anterior displacement of the mitral valve was even more pronounced in the patients with SAM (mitral valve position index, 1.57±0.4) com-
Figure 1. Echocardiographic images from serial examinations in a young patient with hypertrophic cardiomyopathy (HCM) who developed dynamic subaortic obstruction. Panels A–D show serial two-dimensional echocardiographic images in the parasternal long-axis plane obtained in diastole. Panels A–D’ are corresponding M-mode echocardiograms that have been included to show presence or absence of systolic anterior motion (SAM). Panel E is a systolic stop-frame image in long-axis plane obtained at the most recent evaluation, and panel E’ is the corresponding continuous-wave Doppler tracing. Distance between calibration marks represents 10 mm in echocardiograms and 1 m/second in the Doppler tracing. Panels A and A’: At age 12 years, thickness of basal anterior ventricular septum (VS) is 12 mm, left ventricular outflow tract (LVOT) dimension is 18 mm, and SAM is absent. Panels B and B’: At age 14 years, septal thickness has increased to 20 mm, LVOT size is 22 mm, and SAM is still absent. Panels C and C’: At age 15 years, septal thickness has increased to 24 mm, LVOT dimension is 19 mm, and SAM with brief mitral–septal contact (arrow) has appeared. Panels D, D’, E, and E’: At the most recent evaluation (age, 19 years), maximum thickness has achieved 28 mm, LVOT size has decreased to 16 mm, and there is marked SAM and prolonged mitral–septal apposition (arrows). Continuous-wave Doppler interrogation of LVOT (panel E’) demonstrates a waveform typical of obstructive HCM with relatively slow increase in velocity culminating in a delayed peak velocity of 4 m/second in midsystole (estimated gradient is 64 mm Hg).
pared with patients without SAM (index, 0.77±0.2; p<0.005) (Figure 5).

Cardiac Dimensions

At the initial evaluation, left ventricular cavity dimensions were similar in the patients with and without subsequent development of mitral SAM. However, at the most recent evaluation, both left ventricular end-diastolic and end-systolic dimensions were significantly smaller in the patients who developed SAM of the mitral valve during follow-up (Table 2). No difference in left atrial and aortic root dimensions were observed between the groups at either the initial or the most recent evaluation (Table 2).

Clinical and Demographic Findings

Patients with and patients without development of SAM did not differ regarding age at the initial (11.1±2 versus 11.1±3 years) or most recent evaluation (17.5±3 versus 18.1±4 years), duration of follow-up (6.5±3 versus 7.1±3 years), or the percentage change in body surface area (41±16% versus 48±21%). The number of echocardiographic studies performed during follow-up was similar in patients with and in patients without development of SAM (5.4±3 versus 6.4±3 studies per patient).

Each of the seven patients who ultimately developed SAM had no or only minimal symptoms at the initial evaluation; during follow-up, five of these patients remained asymptomatic, one showed symptomatic progression, and one died suddenly (at age 14 years). Of the 19 control patients who did not develop SAM, 16 had no or only mild symptoms and three had moderate symptoms at the initial evaluation; during follow-up, 15 of these patients remained unchanged, three experienced symptomatic progression, and one died suddenly (at age 17 years).

Two (28%) of the seven patients who developed SAM and five (26%) of the 19 patients without SAM received cardioactive drugs (β-blocker or verapamil) throughout most of the follow-up period (p=NS). However, none of the seven patients who developed SAM was taking cardiac medications at the time of initial echocardiographic examination.

Genetic transmission of HCM in first-degree relatives was documented for five of the seven patients who developed SAM and in 17 of the 19 controls (p=NS); however, systematic echocardiographic studies were not performed in all pedigrees.

Discussion

Dynamic subaortic obstruction, an important determinant of clinical course in HCM, results in the vast majority of instances from midystolic apposition of the mitral valve with the ventricular septum. Although outflow obstruction has been identified at virtually any age, including infancy, childhood, and adulthood, the timing of onset and the determinants of evolving subaortic obstruction caused by SAM are largely undefined.

Development and determinants of subaortic obstruction. The present investigation describes the de novo development of SAM between 15 and 19 years of age in a group of patients with HCM followed with serial echocardiography for 3–12 years. The process of development of SAM (and subaortic obstruction) in these patients appeared to result from a dynamic remodeling of left ventricular geometry during a period of rapid body growth and maturation. When initially evaluated, these patients already demonstrated small left ventric-
ular outflow tract dimension and anterior displacement of the mitral valve within the cavity. Subsequently, during follow-up, the left ventricular cavity failed to increase normally in size and the outflow tract narrowing became even more pronounced. This progressive narrowing of the outflow tract was associated with further anterior displacement of the mitral valve within the cavity as well as a disproportionate increase in the thickness of the basal anterior ventricular septum.

In this regard, the seven study patients who developed SAM and subaortic obstruction (as well as 16 of the 19 control patients with HCM who did not) showed a striking increase in overall left ventricular wall thickness during follow-up. Of note, however, those patients who developed SAM showed a particular disproportionate increase in the thickness of the basal portion of anterior septum in contrast to those patients without development of SAM and subaortic obstruction who showed a substantial and predominant increase in the distal portion of ventricular septum below mitral valve level. These findings suggest that it is not the progression of left ventricular hypertrophy per se that is a determinant of outflow obstruction but rather the precise location of the predominant wall thickening process. Furthermore, analysis of the temporal sequence of events in the study patients who developed SAM demonstrated that the greatest increase in basal anterior septal thickness preceded the appearance of marked SAM, suggesting that such selective and disproportionate increase in wall thickness may have played a causal role in the development of outflow obstruction.

**Implications.** The findings of our study have important clinical and pathophysiological implications. First, the demonstration that SAM and dynamic subaortic obstruction may be absent at the initial evaluation of young patients with HCM but can subsequently develop indicates that definite assessment regarding the presence or absence of subaortic obstruction cannot be made in an individual patient until full body growth and maturation are achieved; furthermore, because left ventricular outflow obstruction is a major determinant of
FIGURE 5. Graph shows mitral valve position index at initial and most recent evaluation in patients with and without development of systolic anterior motion (SAM). At initial evaluation, the mitral valve was positioned more anteriorly within the left ventricular cavity in patients who developed SAM. During follow-up, the mitral valve became displaced even more anteriorly in these patients. In contrast, mitral valve position did not change significantly during follow-up in patients without development of SAM. Therefore, the anterior displacement of the mitral valve in patients who developed SAM was even more pronounced at the most recent evaluation.

clinical course in HCM, this observation emphasizes the importance of serial echocardiographic evaluations in young patients with this disease. Second, our findings that marked thickening of the basal anterior septum and reduction in left ventricular outflow tract dimension differentiate children who will from those who will not develop dynamic subaortic obstruction highlight the importance of these morphological features as determinants of left ventricular outflow tract obstruction in HCM and are consistent with previous observations in adult patients with this disease.\(^5,^{24}\)

**Limitations.** The present study is necessarily retrospective. Given the substantial time required to identify development of subaortic obstruction de novo in a sizable group of young patients, it would have been impractical to attain such data prospectively. Certain limitations of our study are, therefore, related to its retrospective nature. For example, we established the age of \(\leq 15\) years at initial evaluation and a minimum follow-up of 3 years as selection criteria for entry into the study in concert with our underlying hypothesis that if SAM developed in patients with HCM, it would likely occur during a period of life that is characterized by marked changes in left ventricular wall thickness and geometry.\(^{14,15}\) As a consequence of these selection criteria, we encountered some variability among the study patients regarding their ages at the initial (5–15 years) and most recent (8–25 years) evaluations; nevertheless, most importantly, patients with and without development of subaortic obstruction were comparable in age at the initial or most recent evaluation and the duration of follow-up.

Our observations regarding the development of outflow obstruction are unavoidably based on a relatively small number of patients. This is due to the fact that HCM is an uncommon disease, it is less commonly identified in children than in adults, and the majority of HCM patients do not develop subaortic obstruction.\(^1\) For this reason, we cannot be certain that our findings regarding the mechanisms by which outflow obstruction develops are applicable to all patients with the obstructive form of HCM. Nevertheless, the ultimate morphological appearance of the left ventricle in our patients who developed SAM was similar in several important respects to that of most other patients with the obstructive form of HCM, i.e., reduced outflow tract size,\(^5,^{24}\) anteriorly positioned mitral valve,\(^9\) and substantial hypertrophy of the basal anterior septum,\(^19,^{24}\) suggesting that the observations in this report probably describe in large measure the mechanisms involved in the pathophysiology of dynamic outflow obstruction characteristic of most other patients with obstructive HCM.

**Conclusions**

The present study demonstrates that SAM and subaortic obstruction can develop de novo in patients with HCM during the adolescent years. This phenomenon is the consequence of a dynamic process of remodeling in left ventricular geometry characterized by progressive narrowing of the left ventricular outflow tract, anterior displacement of the mitral valve within the cavity, and disproportionate thickening of the basal anterior septum.

### Table 2. Cardiac Dimensions in Patients With and Without Development of Systolic Anterior Motion of the Mitral Valve at Initial and Most Recent Evaluations

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<th>Initial evaluation</th>
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<td>With development</td>
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<td>of SAM (n=19)</td>
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<td>Left ventricle</td>
<td>39.5±5</td>
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<td>(end diastole)</td>
<td>(34–40)</td>
<td>(34–52)</td>
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<tr>
<td>Left ventricle</td>
<td>22.8±4</td>
<td>25.4±4</td>
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<td>(end systole)</td>
<td>(17–28)</td>
<td>(22–36)</td>
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<tr>
<td>Left atrium</td>
<td>36.2±6</td>
<td>34.7±8</td>
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<td>(mm)</td>
<td>(27–44)</td>
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<tr>
<td>Aortic root</td>
<td>24.5±6</td>
<td>25.4±5</td>
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<td>40.4±3</td>
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<td>22.1±3</td>
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SAM, systolic anterior motion of the mitral valve.
tum. These findings may have important implications for the understanding of the pathophysiology of dynamic subaortic obstruction in HCM and also for the natural history and serial clinical evaluation of young patients with this disease.

References
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