Morphologic Characteristics of Hypertrophic Cardiomyopathy of the Elderly With Cardiac Myosin-Binding Protein C Gene Mutations

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Background  Several morphologic distinctions between elderly and young patients with hypertrophic cardiomyopathy (HCM) have been reported. In particular, a crescent-shaped left ventricular (LV) cavity with reversed septal curvature, which is often seen in young patients, is rare in elderly patients. However, those studies were carried out before gene testing became available and heterogeneous causes or age-related changes may have been included. The purpose of this study was to determine the morphologic characteristics of elderly patients with HCM definitely caused by a mutation in the cardiac myosin-binding protein C (MyBPC).

Methods and Results  Twenty-seven patients with HCM caused by MyBPC gene abnormality were evaluated. Patients were divided into an elderly group (≥ 65 years of age, n=8) and a young group (<65 years of age, n=19). LV hypertrophy was milder in the elderly than in the young for maximum LV wall thickness (18±5 mm vs 24±6 mm, p=0.008) and Wigle score (5.7±1.5 vs 7.6±1.6, p<0.005). However, an abnormal crescent-shaped LV was similarly prominent in both groups (75% in the elderly vs 95% in the young, p=NS). None of the elderly patients showed a proximal septal bulge.

Conclusions  An abnormal crescent-shaped LV cavity was frequently present in the elderly as in the young when there are MyBPC mutations. It is possible that this morphologic feature could become useful for determining the etiology of HCM in elderly patients.  (Circ J 2006; 70: 875 – 879)

Key Words: Cardiac myosin binding protein C mutation; Elderly; Hypertrophic cardiomyopathy; Morphology
bution of LVH were also assessed using 2-dimensional images and indices as previously described.\(^7,18\) In the parasternal short-axis plane, the LV was divided into 4 segments: anterior and posterior ventricular septum, and anterolateral and posterior free wall. The greatest wall thickness measured at any site in the LV wall was regarded as the maximal thickness, independent of correction for body surface area, gender, or age. Right ventricular wall thickness was evaluated in the parasternal long-axis view, and a wall thickness of more than 5 mm was defined as hypertrophy. The peak instantaneous LV outflow pressure gradient was estimated by continuous-wave Doppler under basal conditions. A LV outflow gradient \(\geq 30\) mmHg was considered significant. Wigle score was also calculated as previously reported.\(^19\)

Furthermore, we studied the morphologic features according to the report by Lever et al.\(^12\) In brief, (1) septal curvature was evaluated in the apical 4-chamber view (Fig 1). An abnormal convexity of the septum toward the LV cavity was defined as reversed septal curvature, which produced a crescent-shaped LV cavity. Slight concavity toward the LV cavity or a more straight septal contour was considered as normal septal curvature. The latter produced an ovoid LV cavity. (2) Proximal septal bulge was assessed in the parasternal long-axis and apical 4-chamber views, and was defined as a subaortic protuberance of the septum toward the LV outflow tract (LVOT) with the middle and distal septum having normal shape. (3) Mitral annular calcification was also evaluated as an increased echocardiographic density of the mitral annulus.

**Genetic Analysis**

Peripheral blood samples were taken at the time of clinical evaluation, and they were frozen and stored at \(-20\)°C.\(^15\) Deoxyribonucleic acid (DNA) was extracted using a DNA purification kit (No. 51104; Qiagen Inc, Hilden, Germany). In vitro amplification of genomic DNA was performed using the polymerase chain reaction (PCR). Oligonucleotide primers were used to amplify protein-encoding exons of MyBPC. (Information on primer sequences and PCR conditions is available upon request.) Sequencing was performed using a BigDye Terminator Cycle Sequencing Kit (No. 4336774; Applied Biosystems, Foster City, CA, USA). The sequences were analyzed on an ABI PRISM 3100-Avant Genetic Analyzer in accordance with the manufacturer’s instructions. In patients in whom mutation was identified, confirmation was obtained by re-analysis with direct sequencing from a second blood sample.

**Clinical Findings**

Functional class was based upon the New York Heart Association (NYHA) classification. Patients with hypertension were defined as those with blood pressure greater than 140/85 mmHg or those taking anti-hypertensive drugs other than \(\beta\)-blocker and/or calcium antagonist. Electrocardiograms were evaluated for cardiac rhythm, SV1 + RV5 \(\geq 35\) mm as LVH, and presence of giant negative T waves as defined by a depth of \(\geq 10\) mm in the left precordial leads.

**Statistical Analysis**

All data are presented as mean \(\pm\) SD. Student’s t-test was used to compare mean values between 2 groups. The \(\chi^2\) test was also used to compare contingency table data. For tables with small excepted cell frequencies, Fisher’s exact test was used. A p-value <0.05 was considered statistically significant.

**Results**

**Patient Characteristics**

Baseline characteristics and echocardiographic findings of all patients are shown in Tables 1 and 2, respectively. The prevalence of an ovoid-shaped LV was higher in the elderly patients \((\geq 65\) years old) than in the young patients \((<65\) years old) \((38%\ vs 19,\ p=0.09\).

Among the 65 patients, 27 were identified with mutations in MyBPC and a positive phenotype was defined as a hypertrophied, non-dilated LV. The mutations in MyBPC were V592fs/8 (frameshift mutation: a 1-base deletion of a thymidine at nucleotide 11645) in 23 patients, S297X (nonsense mutation: a cytosine to guanine transversion at nucleotide 6239) in 4 patients, and R945fs/105 (frameshift mutation: a 2-base deletion of a cytosine and guanine at nucleotides 18535 and 18536) in 1 patient. Two of the 3 mutations (V592fs/8 and R945fs/105) have previously been described as disease-causing mutations\(^15,20,21\) and one mutation (S297X) was novel. These mutations are thought to be disease-causing based on the presence of the mutation in all affected relatives and the absence of the sequence variation in at least 200 chromosomes from healthy individuals. Patients with mutations in MyBPC were younger than those without \((54\pm16\) years old vs 64\pm14\ years old,
On the other hand, the prevalence of a family history of HCM was more common in patients with a mutation in MyBPC than in those without mutation (67% vs 16%, p<0.0001). The patients with mutations in MyBPC were divided into 2 groups according to age (Table 1). The elderly patients ranged in age from 65 to 83 years (mean 73±7 years, n=8) and the young patients ranged in age from 28 to 61 years (mean 45±11 years, n=19). There was no significant difference in NYHA functional class between the 2 groups and most patients showed no or only mild symptoms. The prevalence of atrial fibrillation and systemic hypertension was significantly higher in the elderly patients than in the young patients. There was no significant difference in the treatment between the 2 groups.

**Echocardiographic Findings**

*LV Wall Thickness and Dimensions (Table 2) Maximum LV wall thickness in the elderly patients ranged from 16 to 22 mm (mean 18±2 mm), and none of them showed extreme LVH (≥30 mm). Maximum LV wall thickness in the young patients was greater (range 17–38 mm, mean 24±6 mm), and 2 young patients showed extreme LVH.*

Distribution of LV hypertrophy

<table>
<thead>
<tr>
<th></th>
<th>All (n=65)</th>
<th>Elderly with mutation (n=8)</th>
<th>Young with mutation (n=19)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized, n (%)</td>
<td>9 (14%)</td>
<td>2 (22%)</td>
<td>2 (11%)</td>
<td></td>
</tr>
<tr>
<td>Diffuse, n (%)</td>
<td>56 (86%)</td>
<td>7 (88%)</td>
<td>17 (89%)</td>
<td></td>
</tr>
<tr>
<td>Wigle score</td>
<td>3.3±2.1</td>
<td>5.7±1.5</td>
<td>7.6±1.6</td>
<td>0.005</td>
</tr>
<tr>
<td>LVOT gradient at rest (&gt;30 mmHg)</td>
<td>14 (22%)</td>
<td>0 (0%)</td>
<td>4 (21%)</td>
<td></td>
</tr>
</tbody>
</table>

LV, left ventricular; Localized, hypertrophy localized to 1 LV segment; Diffuse, hypertrophy involving ≥2 LV segments; LVOT, LV outflow tract.

*Comparison between elderly and young patients with the mutation in the myosin-binding protein C gene.
Abnormal convexity of the septum toward the left ventricular (LV) cavity can be seen as reversed septal curvature, which produces a crescent-shaped LV cavity in addition to a large left atrium.

**Morphologic Characteristics (Table 3)**

A distinct crescent-shaped LV cavity, with reversed septal curvature, was prominent in both groups (ie, 7 (75%) in the elderly and 18 (95%) in the young). An ovoid-shaped LV cavity, with normal septal curvature, was not frequent in either group (ie, 2 (25%) in the elderly and 1 (5%) in the young). Thus, there was no significant difference in the LV shape (crescent vs ovoid) between the 2 groups (Fig 1). Also, none of the elderly patients showed a proximal septal bulge. Right ventricular hypertrophy was predominantly seen in the elderly patients, such as an ovoid-shaped LV cavity and a proximal septal bulge, which produces a crescent-shaped LV cavity in addition to a large left atrium.

**Table 3 Comparison of the Morphologic Characteristics of Elderly and Young Patients With the Mutation**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Elderly (n=8)</th>
<th>Young (n=19)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovoid shaped-LV cavity with normal septal curvature, n (%)</td>
<td>2 (25%)</td>
<td>1 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Crescent shaped-LV cavity with reversed septal curvature, n (%)</td>
<td>6 (75%)</td>
<td>18 (95%)</td>
<td>NS</td>
</tr>
<tr>
<td>Proximal septal bulge, n (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Right ventricular hypertrophy, n (%)</td>
<td>1 (13%)</td>
<td>9 (47%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Mitral annular calcification, n (%)</td>
<td>3 (38%)</td>
<td>0 (0%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>1 (25%)</td>
<td>0 (0%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

LV, left ventricular.

**Discussion**

The results of this study indicate that the previously reported morphologic characteristics of HCM in elderly patients, such as an ovoid-shaped LV cavity and a proximal septal bulge, are not common in the elderly patients with HCM definitely caused by mutations in MyBPC. Moreover, a crescent-shaped LV cavity, which has been reported as the hallmark of HCM in young patients, is predominantly present in both elderly and young patients with HCM caused by mutations in MyBPC.

**Etiology of HCM in the Elderly**

HCM was originally described as a primary myocardial disease that showed significant LVH in the absence of other cardiovascular and systemic diseases capable of producing that magnitude of hypertrophy. Over the past decade, molecular genetic approaches have demonstrated that the main cause of HCM is sarcomere protein gene mutations. However, a previous study reported that elderly-onset HCM showed low positive mutations in sarcomere genes; among 31 patients diagnosed with late-onset HCM who had no known affected relatives, only 7 (23%) had mutations in the sarcomere genes (4 in MyBPC, 2 in cardiac troponin I, and 1 in α-cardiac myosin heavy chain). Gene mutations were not identified in the remaining 24 patients (77%) and the cause of LVH in this group remained unknown. Nevertheless, the molecular basis for some elderly-onset disease indicates that this condition could be a heritable disorder of contractile proteins. The distribution of mutations in HCM of the elderly is strikingly different from that of early-onset HCM. Mutations in MyBPC were reported as the most frequent cause of HCM of the elderly and indeed those mutations were the most frequent in our cohort. Therefore, those are the reason why we specifically analyzed MyBPC in our present study and 27 patients were identified with mutations. Two of the 3 mutations (V592fs/8 and R945fs/105) have previously been described as disease-causing mutations and one mutation (S297X) was new. This nonsense mutation is predicted to result in truncation of the protein. The mutation was present in all affected individuals (data for familial information are available upon request) and absent in at least 200 chromosomes from healthy individuals. Therefore, we concluded this mutation is disease-causing. There were 8 elderly (≥65 years) and 19 young (<65 years) patients, and they were compared for morphologic evaluation.

**Morphologic Characteristics of HCM in the Elderly**

Earlier studies have shown several distinct morphologic characteristics of HCM in the elderly. They reportedly show more predominantly an ovoid LV cavity contour with normal septal curvature, a proximal septal bulge, and mitral...
annular calcification. In contrast, young patients show a crescent-shaped LV cavity and reversed septal curvature. Lever et al reported that 24 (86%) of 28 elderly patients with HCM showed an ovoid-shaped ventricle and that 21 (75%) of 28 young patients showed a crescent-shaped LV cavity. In addition, the prevalence of a proximal septal bulge and mitral annular calcification was higher in the elderly patients than that in the young patients. Lewis et al reported that obstruction in the small LVOT was frequent in the elderly, in addition to an ovoid-shaped LV cavity. However, because of the lack of gene testing, it is possible that patients with heterogeneous causes of HCM or age-related changes were included. In the present study, previously described morphologic characteristics of HCM in the elderly, particularly an ovoid-shaped LV cavity, were not common in elderly patients with HCM caused by mutations in MyBPC. A distinct crescent-shaped LV cavity with reversed septal curvature, which was frequently seen in the young patients (95%), was also prominent in the elderly patients (75%). Also, none of the elderly patients showed a proximal septal bulge. Thus, there was no significant difference between the elderly and young patients in the LV shape.

The results of this study are distinctly different from those of studies carried out before gene testing became available. For the purpose of the present study, elderly patients with HCM caused by mutation in MyBPC were enrolled. Therefore, although the morphologic features in patients with HCM caused by other sarcomere gene mutations are unresolved, a crescent-shaped LV in elderly patients with LVH suggests ‘true’ HCM caused by mutations in MyBPC rather than hypertensive hypertrophy or age-related changes.

Clinical Implication

In the clinical situation, the diagnosis of LVH or mild hypertension in the elderly patient is difficult and thus the shape of the LV may be useful for defining the etiology and therefore lead to prompt management.

Study Limitations

First; the number of study patients was small. Second, gene testing was performed only for mutations of MyBPC. A distinct crescent-shaped LV cavity with reversed septal curvature. Thus, there was no significant difference between the elderly and young patients in the LV shape.

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References