Gated Single-Photon Emission Computed Tomography Detects Subendocardial Ischemia in Hypertrophic Cardiomyopathy

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Background Patients with hypertrophic cardiomyopathy (HCM) sometimes develop subendocardial ischemia (SEI) in the left ventricle (LV). In the present study it was examined whether volumetric variables obtained by gated single-photon emission computed tomography (SPECT) are useful in detecting exercise-induced SEI in patients with HCM.

Methods and Results Exercise 99mTc-tetrofosmin myocardial scintigraphy was performed in 26 HCM patients having non-obstruction and mild hypertrophy with a ventricular septal thickness ≤20 mm. SEI was quantified using software developed previously, and the results were correlated with volumetric variables obtained using Quantitative Gated SPECT software. Exercise-induced percentage change in LV end-systolic volume was higher in 9 HCM patients with SEI (25.8±3.1%) than in 17 patients without (10.0±2.5%, p=0.009), although the percentage change in LV end-diastolic volume was similar in the 2 groups. The receiver-operator characteristics curve of the percentage changes in LV end-systolic volume for the detection of SEI showed that the optimal cutoff was 17%. This cutoff point yielded a good diagnostic value for the presence of SEI with a sensitivity of 89%, specificity 82%, and likelihood ratio 5.04.

Conclusions Gated SPECT technique is useful in detecting SEI during exercise in a select population of HCM patients. (Circ J 2007; 71: 256–260)

Key Words: Gated single-photon emission computed tomography; Hypertrophic cardiomyopathy; Subendocardial ischemia

Patients with hypertrophic cardiomyopathy (HCM) sometimes develop subendocardial ischemia (SEI) in the absence of coronary stenosis1-3 and in such patients it seems to be associated with either a high diastolic pressure in the left ventricle (LV)4 or a high level of B-type natriuretic peptide5 possibly causing the poor prognosis6. Furthermore, SEI may be related to an abnormal blood pressure response during exercise7 which has been considered to be a high risk of sudden cardiac death8.9 Thus, assessment of SEI may be useful in risk stratification of patients with HCM.

In practice, SEI is recognized as transient LV cavity dilation (LVCD) because it occurs with lactate metabolic abnormalities in the absence of significant change in LV cavity size1. Thus, HCM patients have been considered to have SEI if transient LVCD was identified from simple visual assessment of non-gated scintigraphic images1, but this technique may lack objectivity. Gated single-photon emission computed tomography (SPECT) has rapidly become part of routine clinical practice because it enables visualization of the LV end-diastolic and end-systolic volumes, together with myocardial perfusion, through a single working process of imaging. Thus, in the present study we examined whether the volumetric variables obtained by gated SPECT are useful in detecting exercise-induced SEI in patients with HCM.

Methods

Study Population

We studied 26 patients with non-obstructive HCM (21 men, 5 women; mean age 56±10 years) referred to Matsushita Memorial Hospital for rest–stress myocardial perfusion imaging in an outpatient setting. The diagnosis of HCM was based on echocardiographic demonstration of LV hypertrophy without dilation in the absence of any cardiac or systemic disorder that can cause hypertrophy10,11 HCM was diagnosed as non-obstructive when the pressure gradient estimated by echocardiography was <30 mmHg at rest or with provocation by the Valsalva maneuver. All the HCM patients were in normal sinus rhythm without conduction abnormalities, such as bundle branch block, or pacemaker implantation; none had valvular heart disease or coronary stenosis with a diameter reduction ≥25% on angiography. Furthermore, all the HCM patients had asymmetric septal hypertrophy with a maximum wall thickness of ≤20 mm. This selection was based on the results of a study of cardiac phantom modifying HCM with asymmetric septal hypertrophy by Nishimura et al12 who found that the difference between the LV volume obtained by gated SPECT and the actual LV volume was within 3% when the
maximum wall thickness was \( \leq 20 \) mm, but otherwise it was greater than or equal to 8%. All the HCM patients underwent maximal symptom-limited exercise testing with 99mTc-tetrofosmin myocardial scintigraphy after giving written or oral informed consent.

**Exercise Testing**

All medications were withdrawn for at least 5 half-lives before exercise testing; none of them had taken amiodarone. All the HCM patients underwent maximal symptom-limited exercise testing as previously described.13 In brief, using an electrically operated bicycle ergometer, the exercise workload began with 25 W and was increased by 25 W every 2 min. The peak workload was determined at either the achievement of the maximal predicted heart rate or cessation of exertion because of excessive symptoms or systolic blood pressure of \( \geq 250 \) mmHg. After achieving the peak workload, all patients continued exercise at the same level for an additional 90 s and had a cool-down period \( \geq 1 \) min maintained at an exercise grade of 30 W.

**Scintigraphy**

99mTc-tetrofosmin (370 MBq or 740 MBq; Nihon Medi-Physics Co, Ltd, Nishinomiya, Japan) was injected intravenously 1 min before the termination of exercise or 4 h after exercise. Gated myocardial SPECT images were acquired 30 min after injection of tracer with a single-head, rotating digital gamma camera equipped with a low-energy, high resolution, parallel-hole collimator (Starcam 3000XC/T, GE Medical System, WI, USA). Thirty-two images over a 180 degree anterior arc, divided into 16 frames per cardiac cycle for each projection, were obtained in a matrix of 64x64 pixels. The acquisition lasted 40 s/projection after exercise testing, and 30 s/projection at rest with an energy window of 10% centered at 140 KeV. Neither attenuation nor scatter correction was applied. Volumetric variables, including LV end-diastolic volume, LV end-systolic volume, and LV ejection fraction (LVEF), were assessed by the Quantitative Gated SPECT (QGS) software package (Cedars-Sinai Medical Center, CA, USA). Furthermore, we calculated the percentage changes in volumetric variables from rest to after exercise.

Non-gated projections were created by summing the gated data at each projection into non-gated raw data and then reconstruction by a standard filtered backprojection algorithm with a Butterworth filter (cutoff frequency, 0.45 cycles/pixel; power factor, 10); transaxial images were reconstructed with a ramp filter. Long- and short-axis slices were then produced by axial reorientation. Obtained images were estimated on the short-axis slices at the apical, mid, and basal LV levels in combination with the apical long-axis views. The apical short-axis section was divided into 4 segments (anterior, septal, inferior, and lateral), and 2 other short-axis sections were divided into 6 segments (anterior, anteroseptal, inferoseptal, inferior, inferolateral, and anterolateral). The degree of tracer uptake in each segment was semi-quantified by 2 experienced observers who had no patient information by means of a 4-point scoring system (0= normal uptake, 1= mildly reduced uptake, 2= moderately reduced uptake, 3= severely reduced uptake).14 Disagreements between these observers were resolved by consensus. Summed stress score and summed rest score were calculated by adding the scores of 16 segments in the stress and rest images, respectively. Summed difference score was determined to be the difference between the summed stress and rest scores.15

We quantified SEI using software we had produced previously2,16,17 and added some corrections to it13 based on the non-gated SPECT images. In brief, the LV was divided into 15 short-axis slices. One hundred radii were generated at 3.6-degree intervals from the center of the middle myocardial image of each slice. The area surrounded by the 100 points of maximal count (ie, the subendocardial ischemia index) was determined to be 1.14.

**Echocardiography**

All the HCM patients underwent echocardiographic analysis with a commercially available echocardiograph (SONOS 5500, Philips Medical Systems, Best, The Netherlands). We measured LV end-diastolic diameter, LV
fractional shortening, ventricular septal thickness, posterior wall thickness, end-systolic left atrial diameter, the peak early transmitral flow velocity (E) to peak atrial flow velocity (A) ratio, and the deceleration time of E wave at the level of mitral valve tip.

Statistical Analysis
Categorical variables were compared by chi-square test or Fisher’s exact test. Continuous variables are expressed as mean±SD and were compared using an unpaired Student t-test. SEI index and scintigraphic perfusion and volumetric variables are expressed as mean±SEM and were compared by Mann-Whitney U-test. The Wilcoxon signed ranks test was used to analyze changes in scintigraphic volumetric variables over time within each group. Spearman correlation coefficients were used to determine the correlations of percentage changes in LV end-systolic volume with scintigraphic variables. The receiver-operator characteristics (ROC) curve was analyzed to determine the best cutoff point; this analysis provided optimal sensitivity and specificity in predicting SEI. A p-value <0.05 was considered statistically significant.

Results

Basic Features
Exercise was discontinued in 11 patients with HCM: 6 because of excessive leg fatigue, 3 with dyspnea, 1 with chest pain, and 1 with systolic blood pressure ≥250 mmHg. None of them developed frequent premature beats defined as ≥10% of all beats during gated SPECT, which will interfere with the accuracy of image acquisition. The SEI index in all the HCM patients was 1.06±0.02, ranging from 0.90 to 1.36; 9 patients were quantitatively diagnosed as having SEI. As shown in Table 1, HCM patients with and without SEI were well matched with respect to baseline characteristics except for left atrial diameter and scintigraphic perfusion variables.

QGS Analysis
Changes in LV end-diastolic volume, LV end-systolic volume, and LVEF from rest to after exercise are shown in Fig 2. The percentage changes in LV end-systolic volume and LVEF differed between HCM patients with and without SEI, with a greater difference in LV end-systolic volume (Fig 3). Furthermore, the percentage change in LV end-systolic volume was significantly correlated with the SEI index (r=0.54, p=0.005) but not with the summed stress score (r=0.13, p=0.5, summed rest score (r=0.34, p=0.11), or summed difference score (r=0.18, p=0.39). The ROC curve of the percentage changes in LV end-systolic volume for the detection of SEI showed that the optimal cutoff was 17% (Fig 4), which yielded a good diagnostic value for the presence of SEI (sensitivity of 89%, specificity 82%, accuracy 85%, positive likelihood ratio 5.04; 95% confidence interval, 1.76 to 14.43), and negative likelihood ratio 0.13 (95% confidence interval, 0.02 to 0.87).

Table 1 Baseline Characteristics of HCM Patients With and Without SEI

<table>
<thead>
<tr>
<th></th>
<th>With SEI (n=9)</th>
<th>Without SEI (n=17)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>57±10</td>
<td>56±9</td>
</tr>
<tr>
<td>Men</td>
<td>7 (78%)</td>
<td>14 (82%)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.4±3.3</td>
<td>24.4±3.1</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td></td>
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<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>47±4</td>
<td>44±5</td>
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<tr>
<td>LV fractional shortening (%)</td>
<td>39±6</td>
<td>38±7</td>
</tr>
<tr>
<td>Ventricular septum wall thickness (mm)</td>
<td>18±2</td>
<td>17±2</td>
</tr>
<tr>
<td>Posterior wall thickness (mm)</td>
<td>11±4</td>
<td>10±1</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>42±5*</td>
<td>38±3</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.0±0.4</td>
<td>1.0±0.4</td>
</tr>
<tr>
<td>Deceleration time (ms)</td>
<td>262±77</td>
<td>260±95</td>
</tr>
<tr>
<td>Exercise testing</td>
<td></td>
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<tr>
<td>Maximum workload (W)</td>
<td>97±23</td>
<td>112±27</td>
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<tr>
<td>Double product</td>
<td>25,356±7,011</td>
<td>27,679±6,778</td>
</tr>
<tr>
<td>Maximum heart rate (beats/min)</td>
<td>128±12</td>
<td>132±12</td>
</tr>
<tr>
<td>ST-segment depression &gt;0.1mV</td>
<td>3 (33%)</td>
<td>7 (41%)</td>
</tr>
<tr>
<td>Scintigraphic perfusion variables</td>
<td></td>
<td></td>
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<tr>
<td>Summed stress score</td>
<td>8.3±3.8*</td>
<td>2.4±1.1</td>
</tr>
<tr>
<td>Summed rest score</td>
<td>3.6±0.9*</td>
<td>1.1±0.5</td>
</tr>
<tr>
<td>Summed difference score</td>
<td>4.7±3.3*</td>
<td>1.3±0.6</td>
</tr>
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Values are mean±SD or n (%).
HCM, hypertrophic cardiomyopathy; SEI, subendocardial ischemia; LV, left ventricular.
*p<0.05 vs HCM patients without SEI.

Fig 2. Changes in left ventricular (LV) end-diastolic volume, LV end-systolic volume, and LV ejection fraction from rest to after exercise (Ex) in hypertrophic cardiomyopathy patients with or without subendocardial ischemia (SEI). Horizontal lines indicate mean±SD.
Visual Assessment

Transient LVCD on simple visual assessment of non-gated scintigraphic images was present in 8 patients, of whom 5 were diagnosed as having SEI. The SEI index was higher in HCM patients with transient LVCD (1.14±0.04) than in patients without (1.02±0.02, p=0.004). Visual assessment was useful in detecting SEI, with a sensitivity of 56%, specificity 82%, accuracy 73%, positive likelihood ratio 3.15 (95% confidence interval, 0.97 to 10.26), and negative likelihood ratio 0.54 (95% confidence interval, 0.25 to 1.16).

Discussion

QGS software developed by Germano et al.\textsuperscript{19} detects the LV endocardial border automatically, but allows manual operator interaction if needed.\textsuperscript{18,19} QGS-derived volumes have a good correlation with volumetric variables assessed by echocardiography, radionuclide ventriculography, and X-ray contrast ventriculography, with high reproducibility.\textsuperscript{20,21} In the present HCM patients, the volumetric variables obtained by QGS analysis were more valuable for diagnosing exercise-induced SEI than simple visual assessment. Furthermore, owing to the automatic process of the method, the determination of the presence or absence of SEI may be more objective and therefore more reliable. In clinical practice, the widespread commercial availability of QGS software will enable easy and convenient diagnosis of SEI in HCM patients.

The algorithm of the QGS software uses Gaussian fit to determine the endocardial border\textsuperscript{19} which may make it difficult to trace the border accurately under some circumstances. The presence of hypertrophy has been reported to cause erroneous tracing\textsuperscript{20} and this technical problem has so far placed a restriction on the application of QGS analysis to HCM patients. In the present study, however, we selected HCM patients having mild hypertrophy with ventricular septal thickness ≤20 mm. In the hearts of this category, a good correlation has been reported between absolute values and QGS-derived volumes according to a study on cardiac phantom modifying HCM.\textsuperscript{12} The presence of significant perfusion defect may also cause possible technical error in tracing the endocardial border\textsuperscript{22,23} In our study, only 3 patients showed a moderate or severe myocardial perfusion abnormality defined as summed stress score ≥9\textsuperscript{24} and the exclusion of these 3 patients did not alter our results.

It may be difficult for QGS software to detect the endocardial border because of partial-volume effects, particularly when small hearts are imaged\textsuperscript{25} Ford et al. studied a set of mathematic digital LV phantoms, and reported that QGS analysis was not accurate enough to examine their heart models with LV end-diastolic volume <70 ml\textsuperscript{26} LV end-diastolic volume at rest and/or after exercise was below 70 ml in 4 of the present HCM patients (Fig 1) and QGS-derived volumetric variables could not detect the presence or absence of SEI in 2 of them because of a relatively low sensitivity and specificity. The QGS software should be employed cautiously for detecting SEI in patients with a small heart.

Study Limitations

The present study population was a highly selected patient group and may not have been large enough. Therefore, the present technique and results can be neither extended nor applied to all patients with HCM. It remains to be elucidated whether similar results are obtained by means of other available programs of gated SPECT analysis in other populations. The proposed mechanisms for myocardial ischemia in HCM are structural abnormalities of the intramyocardial small coronary arteries, an inadequate capillary density relative to the increased myocardial mass, large vessel coronary artery spasm, systolic compression of the septal perforator artery, diastolic dysfunction, and/or LV outflow tract obstruction;\textsuperscript{3,27} however, the distribution remained unknown in our HCM patients. Coronary stenosis defined as a diameter reduction ≥25% on angiography was one of the exclusion criteria in the present study, but \textsuperscript{99mTc}Tetrofosmin myocardial scintigraphy and cardiac catheterization were not performed at the same time in our HCM patients.


Conclusion
Gated SPECT technique is useful in detecting SEI during exercise in a select population of HCM patients.

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References


