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(Citation)

The Kobe journal of the medical sciences, 59(3):81-92

(Issue Date)

2013

(Resource Type)

departmental bulletin paper

(Version)

Version of Record

(JaLCD0I)

<https://doi.org/10.24546/81005262>

(URL)

<https://hdl.handle.net/20.500.14094/81005262>



## Myocardial Impairment Detected by Late Gadolinium Enhancement in Hypertrophic Cardiomyopathy: Comparison with 99mTc-MIBI/Tetrofosmin and 123I-BMIPP SPECT

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Received 27 February 2013/ Accepted 18 March 2013

**Key words:** Magnetic resonance imaging (MRI), late gadolinium enhancement (LGE), single photon emission computed tomography (SPECT), Hypertrophic cardiomyopathy (HCM), myocardial fibrosis

## ABSTRACT

**Purpose:** Myocardial fibrosis is considered to be an important factor in myocardial dysfunction and sudden cardiac death in hypertrophic cardiomyopathy (HCM). The purpose of this study was to compare myocardial fibrosis detected by late gadolinium enhancement (LGE) on cardiac MRI with myocardial perfusion and fatty acid metabolism assessed by single photon emission computed tomography in HCM.

**Materials and Methods:** We retrospectively evaluated 20 consecutive HCM patients (female, 7; mean age, 53.4 years) who underwent LGE, technetium-99m methoxyisobutylisonitrile/tetrofosmin ( $^{99m}\text{Tc}$ -MIBI/tetrofosmin), and iodine-123 beta-methyl-iodophenylpentadecanoic acid ( $^{123}\text{I}$ -BMIPP) imaging. We calculated the myocardium-to-lumen signal ratio (M/L) for LGE in 17 segments based on the American Heart Association statement. Scoring of  $^{99m}\text{Tc}$ -MIBI/tetrofosmin (PI) and  $^{123}\text{I}$ -BMIPP (BM) was performed for each segment using a 5-point scale (0, normal; 4, highly decreased).

**Results:** Nineteen of 20 patients (95%) and 153 of 340 segments (45%) showed LGE. M/Ls were  $0.42 \pm 0.16$ ,  $0.55 \pm 0.17$ , and  $0.65 \pm 0.24$  in PI0/BM0, PI0/BM1-4 and PI1-4/BM1-4, respectively. All M/Ls were significantly higher than that of a normal control ( $0.34 \pm 0.14$ ) ( $p < 0.001$ ).

**Conclusions:** Myocardial fibrosis in HCM can occur despite normal perfusion and fatty acid metabolism, and is more strongly associated with disorders of fatty acid metabolism than with perfusion abnormalities. M/L may be a useful indicator of disease severity.

## INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder, characterized by asymmetric left ventricular hypertrophy with disarray of cardiomyocytes. Patients with HCM usually have preserved cardiac function and relatively good prognosis; however, they occasionally develop decreased cardiac function, heart failure, arrhythmia, or sudden cardiac death. Various patterns of myocardial fibrosis are observed (1), and fibrosis is thought to contribute to the cardiac dysfunction mentioned above (2, 3).

HCM patients exhibit small intramural coronary artery dysplasia (SICAD). This change may lead to decreased perfusion (4), impaired coronary flow reserve (5, 6), prolonged ischemia and myocardial fibrosis as the disease progresses (7).

Late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) has come to play an important role in the diagnosis and risk stratification of HCM. In previous reports the extent of LGE has been linked with progressive disease and markers of clinical risk for sudden death (8). The gadolinium contrast agents currently used for LGE distribute into the extracellular space, and LGE-positive regions in HCM represent increased myocardial collagen (9, 10).

On the other hand, in single-photon emission computed tomography (SPECT), perfusion imaging using  $^{99m}\text{Tc}$ -sestamibi (MIBI) and  $^{99m}\text{Tc}$ -tetrofosmin is usually performed to detect myocardial ischemia in HCM (11-13). In addition, myocyte fatty acid metabolism is visualized by iodine-123 beta-methyl-iodophenylpentadecanoic acid (BMIPP) accumulation. Impairment of fatty acid uptake in HCM can occur prior to myocardial perfusion abnormalities (14, 15).

Although both LGE and SPECT are useful to detect myocardial impairment in HCM, comparison between the modalities was not done sufficiently. The purpose of this study was

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to compare myocardial impairment detected by LGE with myocardial perfusion and fatty acid metabolism by SPECT in patients with HCM.

### MATERIALS AND METHODS

Our institutional review board approved this study. Because of its retrospective design, we did not obtain subjects' written informed consent. None of the authors have any conflicts of interest to disclose with regard to this study.

#### Study population

We retrospectively reviewed 20 consecutive HCM patients (7 female, 13 male; mean age of 53.4 years old) who underwent CMR and 99mTc-MIBI/tetrofosmin and 123I-BMIPP SPECT from April 2006 to December 2009 (Tab. I). The median interval between the first and last examinations was 6.0 days (range, 1 to 211 days). The diagnosis of HCM was made on the basis of clinical, echocardiographic, and hemodynamic features, according to established criteria (16, 17). The study population included seven cases with the dilated phase of HCM, diagnosed based on echocardiographic findings of progressive left ventricular wall thinning and cavity dilatation, 14 cases satisfied criteria of asymmetric septal hypertrophy on the left ventricular short-axis cine MRI image (the ratio of the interventricular septal thickness to left ventricular posterior wall thickness was more than 1.3) (18), and three cases satisfied criteria of apical hypertrophy (the wall thickness at the apical level was more than 15 mm and the ratio of maximal wall thickness at the apical level to that at the basal level was more than 1.3) (19). No patients had undergone surgical procedures, including percutaneous transluminal septal myocardial ablation and myectomy, or had a history of severe hypertension, aortic valve stenosis, or suspicion of other infiltrative diseases such as cardiac amyloidosis. No patient had adverse events between three examinations.

#### Cardiac MRI

We performed CMR using a standardized clinical protocol on a 1.5 T system (Magnetom Sonata, Siemens) with a four-channel surface coil.

We acquired a segmented true-FISP cine sequence (TE 1.3 ms, TR 2.6 ms, flip angle 60 degrees, slice thickness 6 mm, gap 4 mm, in-plane resolution 1.6 x 1.6 mm) with multiple breath holds. Prospective electrocardiogram (ECG) gating was performed using the R wave as a trigger. Nine to 12 short axial sections were obtained to cover the entire left ventricle.

We performed LGE using a segmented inversion-recovery-prepared true-FISP sequence with ECG triggering at 10 minutes after administration of 0.15 mmol/kg of Gadolinium-DTPA (Magnevist, Bayer Schering Pharma). We acquired LGE data at the mid-diastolic phase with a TI of 300 ms. Seven short (10-mm interval) and three long (vertical long axis, 4-chamber, 3-chamber) axial sections were obtained during a single breath hold at each time point. Other imaging variables included the following: segmentation number 65, TE 1.73 ms, flip angle 60 degrees, field of view 340 x 255 mm, matrix 256 x 129, and voxel size 1.3 x 2.0 x 8.0 mm<sup>3</sup>.

#### Myocardial perfusion SPECT

Perfusion imaging was performed using a 600-Mbq dose of 99mTc-MIBI or a 592-MBq dose of 99mTc-tetrofosmin that was administered by intravenous injection at rest, and approximately 30 minutes later SPECT was performed with a dual-head angular rotating gamma camera (VERTEX ADAC Laboratories) equipped with a low-energy

general-purpose collimator. Image acquisition parameters were 180 degrees of rotation (30 steps; 6 degrees per step) using a 64 x 64 matrix and a 20% main window centered at the photopeak energy of  $^{99m}\text{Tc}$  (140 keV). At each projection, a total of 16 individual electrocardiographic gated frames were acquired (50 beats per step).

### $^{123}\text{I}$ -BMIPP SPECT

$^{123}\text{I}$ -BMIPP (111 MBq) was intravenously injected into the antecubital vein under resting conditions after an overnight fast. Data were acquired 20 minutes after injection using the same camera as used for perfusion SPECT. Thirty projections using a 64 x 64 pixel matrix and a 20% main window centered at the photopeak energy of  $^{123}\text{I}$ -iodine (159 keV) were obtained over 180 degrees (30 steps; 6 degrees per step, 45 sec per step) in the 159-keV photopeak with a 20% window.

### Image analysis

For each patient the LGE image used for analysis was that obtained 10 minutes after contrast agent administration. This image was divided into 17 segments according to the American Heart Association statement (20). We set fan-shaped regions of interest (ROIs) covering the area from the subendocardium to the subepicardium in each segment, and set circular ROIs on the blood pool in the left ventricular lumen close to the myocardium of each segment (Fig. 1). We then calculated the myocardium-to-lumen signal ratio (M/L) at each segment, defined as the segment-based M/L. For the patient-based analysis, we calculated the mean M/L of the 17 segments. Left ventricular ejection fraction (LVEF) was measured from the cine images using Simpson's method (Argus analysis program, Siemens). The wall thickness of each segment was measured in the short axis (segment 1 to 16) and vertical long axis (segment 17) cine imaging planes.

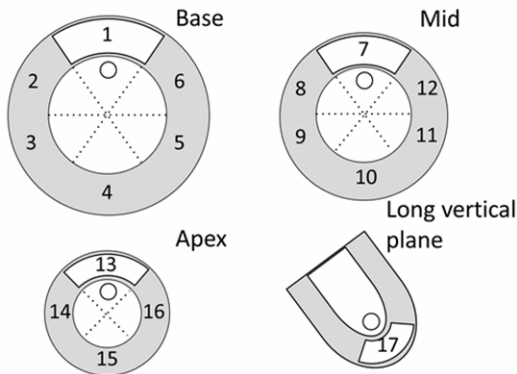


Figure 1.

Scheme of 17-segment model and myocardium-to-lumen signal ratio (M/L) measurement. In accordance with the American Heart Association's 17-segment model, we set a fan-shaped ROI in the myocardium and a circular ROI in the left ventricular lumen. ROIs in the anterior segments at each level and in the apical segment are shown as an example. M/L was calculated for each segment.

As with the LGE image, the  $^{99m}\text{Tc}$ -MIBI/tetrofosmin and  $^{123}\text{I}$ -BMIPP SPECT images were divided into 17 segments each. A five-point scoring system based on visual interpretation was used as follows: 0= normal uptake; 1= slightly decreased uptake; 2= moderately decreased uptake; 3= severely decreased uptake; 4= no uptake, or image defect. Two observers who were unaware of the clinical findings scored the segments by consensus. Observer 1 (H.H.) had 8 years of experiences and observer 2 (K.K.) had 16 years of experiences. The scores of each segment in the perfusion imaging ( $^{99m}\text{Tc}$ -MIBI/tetrofosmin) and  $^{123}\text{I}$ -BMIPP imaging were assigned

the labels PI and BM, respectively. The severity scores of BM (SS-BM) and PI (SS-PI) were calculated as the total scores of the 17 segments in the patient-based analysis.

**Statistical analyses**

The data was statistically analysed using GraphPad PRISM version 5.0 (GraphPad Software, Inc.). The unpaired t-test was used appropriately in segment-based analysis. Correlations between M/L, SS-PI, SS-BM, and LVEF were evaluated using patient-based univariate regression analysis. As a control we used the M/L (mean  $\pm$  2SD =  $0.34 \pm 0.14$ ) obtained from a normal subject in our previous study (21). The normal controls consisted of 20 patients with single vessel myocardial ischemia, 29 with conduction abnormalities, and two with left atrial myxoma (21). The same MR imaging as in this study was performed in the total of 51 patients with normal myocardium (21).

**RESULTS**

All 20 patients were available for analysis. Patient characteristics and results are summarized in Table I.

**Segment-based analysis**

No segments were excluded due to artifacts, and 340 segments were included in the analysis. A representative case is shown in Fig. 2. One hundred and fifty-three segments (45%) showed a higher M/L than the mean+2SD of the normal control. Table II shows the relationship between PI, BM, and M/L. Of the total of 340 segments, 200 (59%) showed concordant findings between BM and PI. BM was higher than PI in 107 segments (31%). Segments' mean M/L increased with PI and BM. The mean M/L was significantly higher than that of the normal control ( $0.34 \pm 0.07$ ), even in the segments with a PI of 0 ( $p < 0.0001$ ) and in those with a BM of 0 ( $p < 0.0001$ ).

The 340 segments were categorized into four groups based on the presence or absence of impairments in myocardial perfusion or fatty acid metabolism. The mean M/Ls at PI0/BM0, PI1-4/BM0, PI0/BM1-4, and PI1-4/BM1-4 were  $0.42 \pm 0.16$  ( $n = 155$ ),  $0.40 \pm 0.10$  ( $n = 14$ ),  $0.55 \pm 0.17$  ( $n = 74$ ), and  $0.65 \pm 0.24$  ( $n = 97$ ), respectively (Fig. 3). Mild fibrosis appeared to be present even in the PI0/BM0 group, given that the mean M/L of this group was significantly higher than that of the normal control ( $p < 0.0001$ ).

Table I. Patients characteristics

| Case No | age   | gender | mean M/L  | LGE | SS-PI | SS-BM | arrhythmia | HR (bpm) | LVEF (%) | NYHA | IVS (mm) | LVPW (mm) | subtype of HCM |       |
|---------|-------|--------|-----------|-----|-------|-------|------------|----------|----------|------|----------|-----------|----------------|-------|
| 1       | 46    | M      | 0.43      | (+) | 6     | 7     | no         | 71       | 58       | 1    | 13.9     | 11.1      | ASH            | APH   |
| 2       | 69    | F      | 0.40      | (+) | 2     | 11    | no         | 46       | 51       | 1    | 9.8      | 6.3       |                |       |
| 3       | 51    | M      | 0.52      | (+) | 3     | 12    | no         | 51       | 46       | 1    | 22.0     | 7.0       |                |       |
| 4       | 48    | M      | 0.76      | (+) | 28    | 38    | Af         | 75       | 20       | 3    | 11.1     | 5.4       |                |       |
| 5       | 59    | M      | 0.42      | (+) | 5     | 19    | no         | 42       | 62       | 2    | 16.0     | 8.0       | ASH            | D-HCM |
| 6       | 60    | M      | 0.35      | (+) | 8     | 17    | no         | 65       | 50       | 2    | 17.4     | 9.8       | ASH            |       |
| 7       | 49    | M      | 0.68      | (+) | 44    | 44    | no         | 52       | 22       | 3    | 9.7      | 9.0       | D-HCM          |       |
| 8       | 50    | M      | 0.41      | (+) | 2     | 22    | no         | 68       | 59       | 1    | 14.2     | 9.4       |                |       |
| 9       | 46    | M      | 0.65      | (+) | 1     | 15    | Af         | 73       | 35       | 2    | 16.0     | 15.2      | ASH            | D-HCM |
| 10      | 53    | M      | 0.62      | (+) | 51    | 40    | no         | 70       | 29       | 4    | 11.4     | 5.6       |                |       |
| 11      | 16    | F      | 0.28      | (-) | 22    | 16    | no         | 49       | 57       | 2    | 15.4     | 4.3       | ASH            |       |
| 12      | 22    | F      | 0.35      | (+) | 0     | 4     | no         | 46       | 62       | 1    | 14.7     | 6.0       | ASH            |       |
| 13      | 68    | F      | 0.45      | (+) | 2     | 9     | no         | 52       | 48       | 1    | 13.0     | 5.2       | ASH            | D-HCM |
| 14      | 68    | F      | 0.53      | (+) | 0     | 13    | no         | 70       | 57       | 1    | 10.5     | 8.3       |                |       |
| 15      | 47    | M      | 0.73      | (+) | 27    | 40    | PVC        | 54       | 16       | 1    | 11.7     | 7.0       |                |       |
| 16      | 64    | M      | 0.53      | (+) | 0     | 2     | no         | 58       | 58       | 2    | 14.7     | 10.0      |                |       |
| 17      | 81    | F      | 0.37      | (+) | 0     | 0     | no         | 65       | 63       | 2    | 13.6     | 11.8      | ASH            | D-HCM |
| 18      | 63    | M      | 0.66      | (+) | 8     | 24    | Af         | 52       | 27       | 2    | 14.6     | 8.7       |                |       |
| 19      | 80    | F      | 0.39      | (+) | 1     | 1     | PAC        | 55       | 45       | 2    | 21.6     | 12.6      | ASH            |       |
| 20      | 28    | M      | 0.75      | (+) | 40    | 45    | no         | 69       | 14       | 4    | 15.5     | 15.7      |                |       |
| mean    | 53.4  |        | 0.51      |     | 12.5  | 19.0  |            | 59.2     | 44.0     | 1.9  | 14.3     | 8.8       |                |       |
| range   | 16-81 |        | 0.28-0.76 |     | 0-51  | 0-45  |            |          | 14-63    | 1-4  | 9.7-22.0 | 4.3-15.7  |                |       |

M: male, F: female, M/L: myocardium-to-lumen signal ratio, LGE: late gadolinium enhancement, LGE (+) indicates the patient has segments with a high M/L greater than mean+2SD of normal control, SS-PI: the severity score of  $^{99m}\text{Tc}$  MIBI/tetrofosmin (perfusion imaging), SS-BM: the severity score of  $^{123}\text{I}$ -BMIPP, HR: heart rate, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association heart failure classification, IVS: interventricular septum thickness, LVPW: left ventricular posterior wall thickness, Af: atrial fibrillation, PVC: premature ventricular contraction, PAC: premature atrial contraction, ASH: asymmetrical septal hypertrophy, APH: apical hypertrophy, D-HCM: dilated phase of hypertrophic cardiomyopathy

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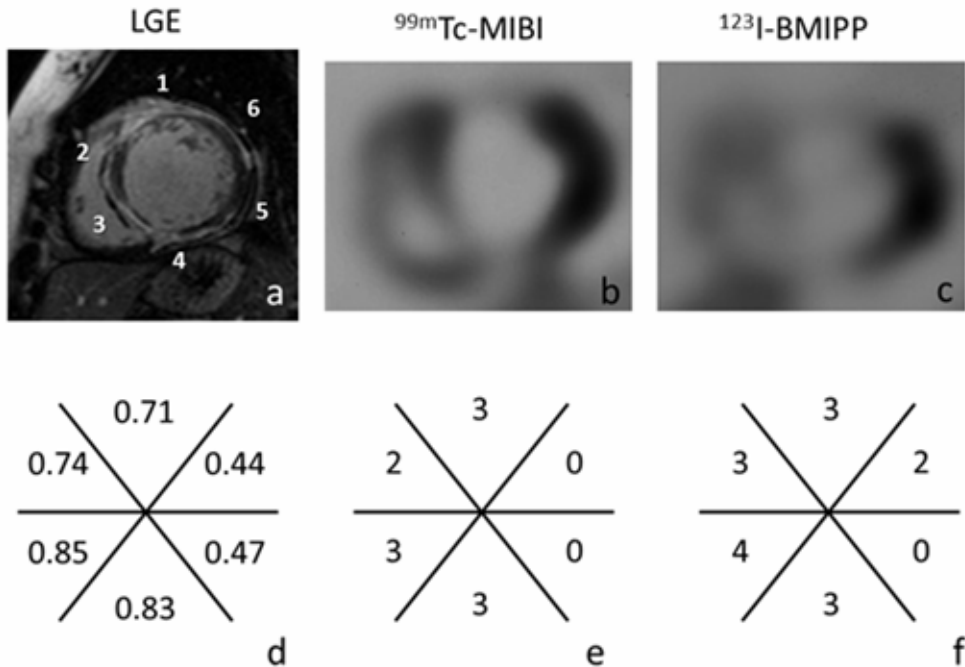


Figure 2.

A representative case of dilated-phase HCM in a 49 year-old female.

Late gadolinium enhancement (LGE) (a),  $^{99m}\text{Tc}$ -MIBI SPECT (b), and  $^{123}\text{I}$ -BMIPP SPECT (c) images at the basal level are shown in the upper column. The lower column shows, for each segment, the M/L value evaluated with LGE (d), the  $^{99m}\text{Tc}$ -MIBI/tetrofosmin score (perfusion imaging, PI; e) and the  $^{123}\text{I}$ -BMIPP score (BM; f). All segments show various degrees of LGE. BM is higher than PI in segments 2, 3, and 6.

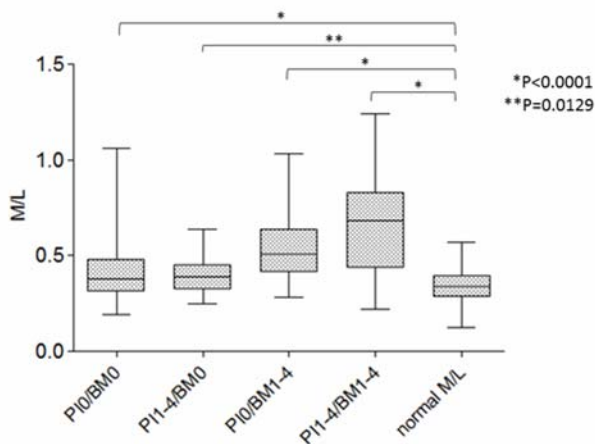


Figure 3.

Box and whisker diagram of myocardium-to-lumen signal ratios (M/L). Patients were divided into four groups based on the presence or absence of SPECT score abnormalities. Each group shows significantly higher M/L than normal controls (\* $p < 0.0001$ , \*\* $p = 0.0129$ ). Normal (control) data were taken from a previous study (21).

### Patient-based analysis

Nineteen of 20 (95%) patients were considered LGE-positive because they had higher M/Ls than the normal control in one or more segments.

The mean M/L correlated significantly with SS-BM ( $r^2 = 0.57$ ,  $p < 0.0001$ ) and SS-PI ( $r^2 = 0.35$ ,  $p = 0.006$ ) (Fig. 4a, b). Although there was a strong correlation between SS-BM and SS-PI ( $r^2 = 0.78$ ,  $p < 0.0001$ ), in the 14 patients with an SS-PI of less than 10, the SS-BM score was higher than the SS-PI score (Fig 4c). The mean M/L and SS-BM correlated well with LVEF (M/L,  $r^2 = 0.74$ ;

SS-BM,  $r^2 = 0.71$ ), while the correlation between SS-PI and LVEF was not as strong (SS-PI,  $r^2 = 0.55$ ) (Fig. 5).

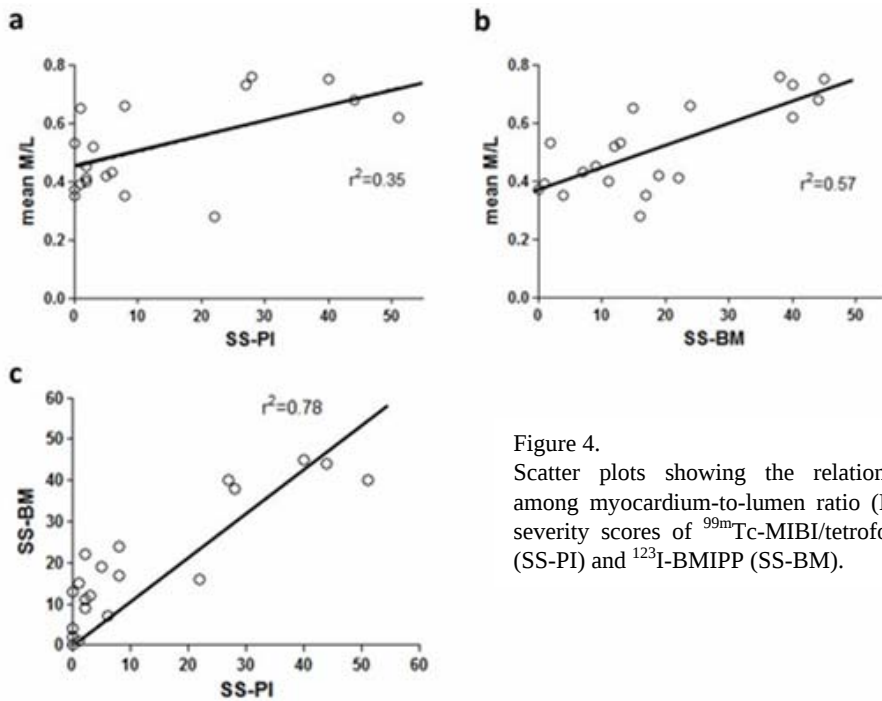


Figure 4.  
Scatter plots showing the relationships among myocardium-to-lumen ratio (M/L), severity scores of  $^{99m}\text{Tc}$ -MIBI/tetrofosmin (SS-PI) and  $^{123}\text{I}$ -BMIPP (SS-BM).

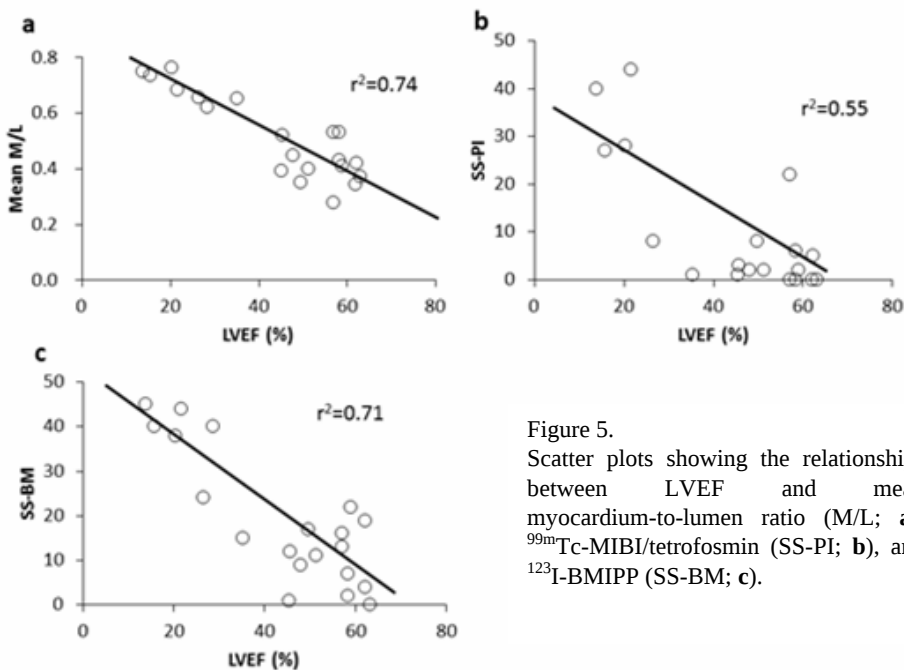


Figure 5.  
Scatter plots showing the relationships between LVEF and mean myocardium-to-lumen ratio (M/L; a),  $^{99m}\text{Tc}$ -MIBI/tetrofosmin (SS-PI; b), and  $^{123}\text{I}$ -BMIPP (SS-BM; c).

## DISCUSSION

Generally, 123I-BMIPP has been considered to be more sensitive than perfusion imaging (99mTc-MIBI/tetrofosmin) at detecting myocardial impairment (14, 15). The results of this study were consistent with this, in that uptake of 123I-BMIPP was equal to or lower than that of 99mTc-MIBI/tetrofosmin in 307 of 340 segments (90%) in the segment-based analysis, and the SS-BM was higher in low-SS-PI patients in the patient-based analysis. Positron emission tomography (PET) is also used to quantitatively evaluate myocardial perfusion, oxidative metabolism, and fatty acid metabolism in cardiac diseases, and enables us to estimate the severity of the disease (22-25). Tadamura reported that the first manifestation of HCM-associated myocardial metabolic abnormalities is considered to be the reduction of 123I-BMIPP uptake followed by the impairment of oxidative metabolism as visualized using acetate-PET (24). Thus, it is thought that reduction of 123I-BMIPP uptake may reflect a functional abnormality, and organic changes in regions with reduced 123I-BMIPP uptake have not been confirmed.

This study demonstrated that the mean M/L was significantly higher in patients than in the normal control, even in segments with PI0/BM0 and PI0/BM1, which suggested that organic changes such as fibrosis can be present in segments with apparently normal perfusion and fatty acid metabolism. In a previous report that compared LGE to 123I-BMIPP and visually assessed LGE, some segments showed decreased uptake of 123I-BMIPP without LGE, while other segments exhibited LGE without decreased 123I-BMIPP uptake (26). Because of the differences in LGE evaluation methods and patient populations, a direct comparison between our results and those of this past report was not performed.

A previous study using the null-point method showed that LGE increased significantly with decreased systolic function, and suggested that substantial LGE in a patient with low-normal LVEF values may be a predictor of disease progression (27). 123I-BMIPP can be an indicator of disease severity, and may predict treatment response or prognosis (28, 29). The high correlation of the mean M/L with SS-BM and LVEF suggests that the mean M/L can serve as a good indicator of global disease severity and prognosis in HCM.

There are several possible sources of error in SPECT. First, weakly damaged myocardium can appear normal in SPECT images, probably because these images are assessed visually and relatively. Second, heterogeneous wall thickening in HCM can be a source of error because of its limited spatial resolution. Third, misalignment between perfusion SPECT and BMIPP SPECT can occur. Of the 169 segments with BM0, 14 segments had mildly decreased perfusion (PI1, n = 13; PI2, n = 1) (Tab. II). Generally, however, impairment of myocardial perfusion does not precede abnormalities in fatty acid metabolism (14, 15). Therefore, the combination of decreased uptake of

Table II. Relationship among PI, BM, and M/L

|            | BM   |      |      |      |      |       | M/L        |
|------------|------|------|------|------|------|-------|------------|
|            | 0    | 1    | 2    | 3    | 4    | total | (Mean±1SD) |
| PI         | 0    | 155  | 35   | 30   | 8    | 1     | 229        |
|            | 1    | 13   | 11   | 6    | 7    | 1     | 38         |
|            | 2    | 1    | 5    | 9    | 9    | 2     | 26         |
|            | 3    | 0    | 2    | 5    | 13   | 8     | 28         |
|            | 4    | 0    | 0    | 2    | 5    | 12    | 19         |
| total      | 169  | 53   | 52   | 42   | 24   | 340   |            |
| M/L        | 0.42 | 0.48 | 0.58 | 0.67 | 0.82 |       |            |
| (mean±1SD) | ±    | ±    | ±    | ±    | ±    |       |            |
|            | 0.16 | 0.17 | 0.21 | 0.19 | 0.20 |       |            |

99mTc-MIBI/tetrofosmin and normal fatty acid metabolism cannot be easily explained, and may be an error caused by overestimation of PI due to visual assessment and misalignment between 99mTc-MIBI/tetrofosmin and 123I-BMIPP SPECT.

In this study, LGE was evaluated using the M/L, which was described in a previous publication (21). The frequency of LGE-positive patients (95%) was higher than that in previous reports (76–88%) (2, 8, 30–32). In the segment-based analysis, 45% of segments were LGE-positive in this study, which was also higher than demonstrated in previous reports, i.e., 14.7% by Conte (31) and 34% by Sotgia (32). These differences may be partially due to patient selection bias. However, the main reason is more likely the differences in the methods used to evaluate LGE. Most previous studies used the null-point method, in which the signal from the least-enhancing region of myocardium is adjusted to null and then used as the reference (suspected “normal” myocardium). Thus, myocardium with weak fibrosis in HCM may not be detected as abnormal when using the null-point method because HCM can demonstrate diffuse fibrosis and myocardial disarray. Measurement using T1 or R1 is effective for quantifying the strength of myocardial enhancement. Messroghli reported a T1-based myocardial mapping technique that used a modified Look–Locker inversion recovery sequence (33). However, T1 mapping is time consuming and requires specific software. In contrast, the M/L does not require dedicated software and multiple images can be obtained with a single breath hold.

This study has several limitations. The number of patients was relatively small, and therefore we did not conduct an analysis of differences among HCM subtypes such as ASH, APH, and dilated HCM. The washout phenomenon in 99mTc-MIBI/tetrofosmin and the heart-to-mediastinum ratio (H/M) in 123I-BMIPP were not evaluated. Determination of whether a segment was LGE positive depended on specific criteria. The M/L depended on magnetic field strength and the sequence used for LGE.

In conclusion, LGE evaluated using the M/L is well correlated with LV function, 123I-BMIPP SPECT, and perfusion SPECT. LGE can serve as a useful method for detecting myocardial impairment prior to decreases in 99mTc-MIBI/tetrofosmin and 123I-BMIPP SPECT uptake, and may be an indicator of disease severity and prognosis.

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