Cardiac cell damage in hypertrophic cardiomyopathy evaluated by beta-methyl-branched fatty acid analogue, iodine-123-15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) myocardial fatty-acid imaging and late gadolinium-enhanced contrast magnetic resonance imaging: usefulness of combining the two techniques

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Abstract

Background: Late gadolinium-enhanced (LGE) magnetic resonance imaging (MRI) has been found to be a highly valuable imaging modality for myocardial characterization in cases of hypertrophic cardiomyopathy (HCM). In addition, abnormalities of BMIPP uptake have also been recognized in HCM. In this study, we hypothesized that abnormalities of fatty acid uptake and metabolism may be detected before fibrosis can be recognized on cardiovascular MRI in patients with HCM.

Methods and Results: Twenty-four patients with HCM were examined by both BMIPP myocardial fatty acid imaging and LGE MRI, and the results of the two imaging methods were compared. BMIPP uptake abnormalities were recognized in 23 of the 24 HCM patients (95.8%) and 126 out of the 408 segments (30.9%) examined, and were most frequently located in the interventricular septum and anterior wall of the left ventricle, the inferior wall and apex of the heart. Areas of LGE were recognized in 18 of the 24 HCM patients (75%) and 50 of the 408 segments (12.2%) examined, and were most frequently located in the interventricular septum of the left ventricle. Double-positive results of both BMIPP uptake abnormalities and LGE were recognized in 18 of the 24 cases (75.0%) and 45 of the 408 segments (11.0%) examined. Double-positive results were noted most frequently in the interventricular septum of the left ventricle and the anterior wall.

Conclusion: The areas showing BMIPP uptake abnormalities were more extensive than those showing LGE on MRI. In addition, the positivity rate for BMIPP uptake abnormalities in areas showing LGE on MRI was considerably higher than that of LGE positivity in areas positive for BMIPP uptake abnormalities. These results are not contradictory to our hypothesis. Therefore, differences between the examination methods in terms of the extent and positivity rate in cases of HCM may be related to the stage of progression of the cardiac muscle cell damage in cases of HCM. Thus, the use of both examinations together might be useful in the evaluation of the stage of disease progression in cases of HCM.
Introduction

Cardiovascular magnetic resonance imaging (MRI) has been reported as a useful imaging modality for observation of the cardiac morphology and has shown high reproducibility in cardiac function analyses. In addition, late gadolinium-enhanced (LGE) MRI has also been shown to be highly valuable for the detection of infarcted myocardium and the prediction of the post-infarct myocardium viability in cases of ischemic heart disease\(^\text{12}\). Abnormalities have been reported to be observed at a high frequency on LGE-MRI in cases of hypertrophic cardiomyopathy (HCM). More recently, it was demonstrated that areas showing LGE on the MR images in these cases corresponded to areas of myocardial fibrosis as assessed by histopathological examination\(^\text{3}\). On the other hand, BMIPP (\(^{123}\)I-15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid) myocardial fatty acid imaging is a nuclear imaging modality used to evaluate changes of the fatty acid metabolism in myocardial cells. BMIPP uptake abnormalities are known to arise from disordered fatty acid metabolism in ischemic heart muscle\(^\text{4}\). In addition, BMIPP uptake abnormalities have also been frequently recognized in cases of HCM, and in these cases also, the abnormalities are assumed to arise from disordered cardiac muscle cell fatty acid metabolism\(^\text{5}\). While several mechanisms have been proposed to explain the pathogenesis of cardiac muscle cell damage in cases of HCM, no consensus has been arrived at\(^\text{6}\). Reports comparing the results of LGE-MRI with those of BMIPP myocardial fatty acid imaging in cases of HCM are almost non-existent\(^\text{7}\). We hypothesized that abnormalities of fatty acid uptake and metabolism as evaluated by BMIPP imaging may be detected even before fibrosis can be recognized as positive enhancement on LGE MR images in patients with HCM. Therefore, in this study, we compared the results of LGE-MRI with those of BMIPP myocardial fatty acid imaging in cases of HCM, and reviewed the usefulness of combining the two imaging methods to evaluate the stage of progression of cardiac muscle cell damage in cases of HCM.

Methods

Twenty-four patients (17 men and 7 women; average age, 57.4±11.9 years) with hypertrophic cardiomyopathy participated in the study, and were examined by both BMIPP myocardial fatty acid imaging and LGE-MRI at Tokyo Medical University Hospital during the five-year period from April 2001 to April 2006. Both examinations were performed within one month of each other. Informed consent was obtained from all of the patients and/or their families for participation in the study.

| Table 1 Patients’ clinical characteristics |
|------------------|------------------|
| Age              | 57.4±11.9        |
| Male/Female      | 17/7             |
| symptoms         |                  |
| dyspnea          | 8                |
| chest pain       | 2                |
| chest oppression | 2                |
| faintness        | 2                |
| presyncope       | 1                |
| none             | 9                |
| Findings of MRI  |                  |
| EDV (ml)         | 81.7±27.3        |
| EF (%)           | 61.0±18.5        |
| LV mass (g/m²)   | 179.1±70.9       |
| Holter ECG       |                  |
| VT (+)/VT (−)    | 6/18             |
| Findings of UCG  |                  |
| A/E              | 1.17±0.44        |
| Neurohormonal factors |            |
| BNP (pg/ml)      | 208.7±247.6     |

CMR, cardiovascular magnetic resonance; EDV, end-diastolic volume; EF, ejection fraction; LVM, Left ventricular mass; ECG, electrocardiogram; VT, ventricular tachycardia; UCG, echocardiography; A/E, atrial contraction wave/early diastolic wave.

In all subjects, the cause of the myocardial hypertrophy was somewhat unclear, and the diagnosis of HCM was based on the presence of LV hypertrophy without cavity dilatation (maximum wall thickness ≥15 mm), as well as the absence of other cardiac or systemic disease capable of producing the degree of hypertrophy evident in each patient\(^\text{8,10}\). In addition, coronary angiography revealed no coronary artery lesions in any of the patients, and secondary myocardial disease was ruled out through a myocardial biopsy. Old myocardial infarction, end-stage HCM, and apical hypertrophic cardiomyopathy were ruled out by careful history-taking. The subjects’ clinical backgrounds are shown in Table 1. We reviewed the status of the areas that were negative on LGE-MRI but positive for BMIPP uptake abnormalities on SPECT; the final decision of a positive or negative rating was reached through consensus among 3 independent cardiologists blinded to other study data.

BMIPP Myocardial Fatty Acid Imaging.

Myocardial fatty acid imaging was performed using a \(^{123}\)I-BMIPP system (Nihon Mediphysics, Nishinomiya, Japan). After the patient had fasted overnight, 111 MBq of \(^{123}\)I-BMIPP was administered intravenously while the patient rested, and the imaging scans were acquired 20–30 min after the injection\(^\text{11}\). Data were acquired with a 2- or 3-detector gamma camera equipped with a low-energy high-resolution parallel multi-hole collimator (Prism 2000XP or Prism 3000XP, Picker; Cleveland,
Cardiovascular MRI protocol

Cardiovascular MR imaging was performed with a Magnetom Avanto and Magnetom Symphony (Siemens, Erlangen, Germany, 1.5T whole-body MR system). A phased-array body coil and spine coil were used, with the subject in the supine position. After localizations, cine segmented balanced steady-state free precession images were acquired for long-axis, short-axis and 4-chamber views. The typical scan parameters are shown in Table 2. For each slice, single-slice imaging was acquired during a single breath-hold. In the long-axis cine image, 8 to 10 slices of the short-axis view and 4-chamber view images were captured using the steady-state free precession method. The cardiac function analysis was input into the integral work station Argus together with 8-10 short-axis slices taken at intervals of 8 mm. LGE imaging was started 10 min after the intravenous administration of gadolinium-DTPA (0.15 mmol/kg, Magnevist, Japan Schering, Osaka, Japan). LGE images were acquired using the inversion-recovery segmented spoiled gradient-echo and phasesensitive inversion recovery methods in long-axis, short-axis and 4-chamber views \(^{(2)}\). For each patient, the optimal inversion time was determined from the T1-Scout sequence which was executed immediately before the LGE imaging. To judge the presence or absence of LGE, we defined regions of interest (ROI) as large as possible in each segment of the myocardium and calculated the signal intensity in each segment. As a control, we measured the signal intensity of skeletal muscle at 17 points in the same film. The mean signal intensity of the skeletal muscle was 15.64±2.31. There are some papers in what the value of the signal intensity from non-infarct area is used as control to evaluate myocardial infarction area with LGE-MRI. However, in HCM a small amount of interstitial fibrosis, the area of which is not so hypertoropic is generally recognized. Therefore it is difficult to distinguish apparently normal areas from such areas with small amounts of interstitial fibrosis. We think that it is not suitable to employ myocardium as a control in HCM. Therefore we used the value of signal intensity from skeletal muscles as the control in this study. As in a previous report \(^{(3)}\), we defined a mean signal intensity of the value in the skeletal muscle +2 SD as the threshold value, and defined any segment of myocardium with a signal intensity higher than this threshold as LGE-positive. The mean signal intensity in the LGE-positive segments was 46.1±31.3, while that in the LGE-negative segments was 12.9±5.3, indicating a significant difference between the two \((P<3.55 \times 10^{-5})\).

The assessment of the presence or absence of LGE was conducted in 17 segments in a similar manner to that in the BMIPP myocardial fatty acid imaging.

Continuous data were presented as the average±standard deviation. Paired t-tests were performed to evaluate the differences between groups. Differences with a \(P\) value of <0.05 were considered to be statistically significant. The study protocol was approved by the ethics committee of our institution, and informed consent was obtained from each patient.

### Results

1) Frequency of reduced BMIPP uptake (BMIPP-positive)

We determined that 23 of the 24 HCM patients were BMIPP-positive (95.8%). BMIPP uptake abnormalities were recognized in 126 out of the 408 segments (30.9%) examined, and most frequently in the interventricular septum of the left ventricle and anterior wall (segments 1, 2, 3, 7, 8, 13), the inferior wall (segments 4, 10, 15) and the apex of the heart (segment 17). The distribution of the BMIPP uptake abnormalities in the 17-segment model is illustrated in Fig. 1.

2) Frequency of enhancement on LGE-contrast MRI (LGE-positive)

We recognized LGE-positive areas in 18 of the 24 HCM patients (75%). Enhancement was recognized in 50 of the 408 segments (12.2%) examined, most frequently in the interventricular septum of the left ventricle.
Let us examine the distribution of the BMIPP uptake abnormalities in the 17-segment model. The distribution of LGE in the 17-segment model is shown in Fig. 2.

3) Comparison of the distribution between BMIPP uptake abnormalities and LGE on MRI.

(a) Patients and segments that were both BMIPP-positive and LGE-positive. (Fig. 3)

Areas that were both BMIPP-positive and LGE-positive were recognized in 18 of 24 cases (75.0%) and 45 of all the 408 segments (11.0%) examined. Double positivity was recognized most frequently in the interventricular septum of the left ventricle (segments 2, 8 and 9) and the anterior wall (segments 7 and 13) (Fig. 4).

(b) Patients and segments that were both BMIPP-positive and LGE-negative. (Fig. 5)

Twenty-one of the 24 cases (87.5%) and 80 of the 408 segments examined (19.6%) showed a combination of BMIPP positivity and LGE negativity. Such BMIPP positive and LGE negative findings were most frequently located in the inferior wall (segments 4, 10, and 15) and the apex of the left ventricle (segment 17) (Fig. 6).

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Fig. 1  Distribution of the BMIPP uptake abnormalities in the 17-segment model.

Fig. 2  Distribution of LGE in the 17-segment model.

Fig. 3  (A): 63-year-old woman, (B): 56-year-old woman. Three short-axial images of LGE and BMIPP are shown. Double positive findings (BMIPP uptake abnormalities + enhancement on LGE-MRI) were recognized.
(c) Patients and segments that were BMIPP-negative (normal BMIPP uptake) and LGE-positive. (Fig. 7)

Two of the 24 patients (8.3%) and 5 of the 408 segments (1.3%) showed a combination of BMIPP negativity and LGE positivity. (Fig. 8)

(d) BMIPP-negative and LGE-negative.

A double-negative result, that is, both BMIPP-negative and LGE-negative, was seen in only one patient.
Discussions

In this study, areas showing BMIPP uptake abnormalities and enhancement on LGE-MR imaging were most frequently recognized in the interventricular septum in the HCM patients. However, the areas showing BMIPP uptake abnormalities were more extensive than those showing enhancement on the LGE-MR imaging. In addition, the frequency of BMIPP-positive cases was higher than that of LGE-positive cases.

In general, BMIPP uptake abnormalities are recognized at a high frequency in HCM patients; this is presumed to be related to the disordered fatty acid metabolism in hypertrophic cardiac muscle cells. BMIPP is a marker of metabolic alteration, because the degree of BMIPP uptake closely reflects the myocardial ATP concentration as well as the mitochondrial and cell membrane functions. Thet-Thet-Lwin et al. reported that the cardiac muscle uptake of BMIPP in a hamster model of cardiomyopathy was lower than that in normal hamsters. In addition, light microscopy and electron microscopy also demonstrated slight interstitial fibrosis and ultrastructural changes in the mitochondria in the hamster model of cardiomyopathy. Okazaki et al. reported using compartment model analysis for human cardiac BMIPP metabolism, that BMIPP SPECT might be useful to detect subtle changes in the fatty acid metabolism of the cardiac muscle cells in patients with HCM, not only for the diagnosis of HCM in its very early stages, but also for the evaluation of its progression. According to Ohtsuki, BMIPP uptake abnormalities are recognized at the highest frequency in the right ventricular attachment area and apex of the heart, and they strongly suspect that disordered fatty acid metabolism in cardiac muscle cells is prominent in these areas.

On the other hand, Kim reported, from a myocardial infarction experiment conducted using a canine model, that LGE-positive areas on MR imaging coincided with the infarct area determined histopathologically. Subsequently, LGE-MRI was reported to be useful for evaluating the characteristics of myocardial infarct lesion and the viability of post-infarct myocardium. On the other hand, in the case of HCM, LGE-positive areas on LGE-MRI are most often recognized at the site of right ventricular attachment of the interventricular septum. In addition, the extent of the LGE-positive area on LGE-MRI has been shown to positively correlate with the myocardial wall thickness, and negatively correlate with the percent thickening. Furthermore, the extent of the LGE-positive areas on LGE-MRI has been recognized to be greater during the stages of disease progression than after the establishment of fibrosis, and also in cases with multiple risk factors for sudden cardiac death. We had previously demonstrated that in patients with HCM, the LGE-positive areas on LGE-MRI were most frequently recognized at the right ventricle attachment area of the interventricular septum. We also demonstrated a decreased left-ventricular ejection fraction compared with that in cases with extensive LGE-positive areas on LGE-MRI. We also reported that the frequency of positive findings on LGE-MRI and the number of segments showing LGE positivity on LGE-MRI was greater in cases with ventricular tachycardias compared with that in those without ventricular tachycardia.

Kuribayashi et al. reported, based on post-mortem examinations of hearts from HCM patients, that the characteristic histopathological changes, such as myocardial disarray and fibrosis, were most pronounced in the right ventricle attachment area of the interventricular septum. In our study, double-positives (abnormal findings on both BMIPP imaging and LGE-MRI) were mainly observed in these same areas.

On the other hand, areas with BMIPP uptake abnormalities that did not show late enhancement were most frequently found in the inferior wall; this is considered to be attributable to the influence of SPECT attenuation. In areas other than the inferior wall, i.e., areas distant from the influence of SPECT attenuation, the frequency of BMIPP uptake abnormalities in LGE-positive areas was much greater than that of LGE positivity in areas showing BMIPP uptake abnormalities (93% and 44%, respectively). In this study, we hypothesized that abnormalities of fatty acid uptake and metabolism may be detected before fibrosis can be recognized on LGE-MR images in patients with HCM. Difference in the positivity rates between the two examination methods may be related to the stage of progression of the cardiac muscle cell damage in cases with HCM. In other words, our findings suggest that the metabolic disorder in myocardial cells (evaluated by BMIPP) may be detected before the resultant histologic changes during the course of progression of the cardiac muscle cell damage in cases of HCM. This is consistent with our hypothesis.

On the other hand, 2 patients and 5 segments in the present study showed a combination of BMIPP negativity and LGE positivity. In both of the cases, the areas showing this combination of findings were extremely small, and detection of such small areas by SPECT might have been difficult. Wagner et al. reported a diagnostic sensitivity of LGE-MRI and T1 cardiac muscle SPECT for small subendocardial infarctions of 92% and 28%, respectively, and suggested that the extreme difference in spatial resolution between cardiac MRI and SPECT could be the reason behind the inability to recognize BMIPP uptake abnormalities in gadolinium enhancement-positive segments.

The differences in the frequency of positive findings between BMIPP fatty acid metabolic imaging and LGE-MRI were mainly observed in these same areas.
MRI may reflect the stage of progression of the cardiac muscle cell damage in HCM. In cases with large differences in the positivity rates between the two imaging methods, cardiac muscle cell damage may be expected to occur in the future, and this damage can be assessed histologically. The results of our present study suggest that the combined use of the two imaging methods might yield important clinical information to allow identification of cases with a poor prognosis and to estimate the stage of progression of the disease. We further believe that we have demonstrated the importance of combining the in vivo findings of LGE-MRI and BMIPP fatty acid metabolic imaging for understanding the stages in the progression of the cardiac muscle abnormalities in HCM and the relevance of such information in the actual clinical situation.

However, it is necessary to prove this hypothesis with a large number of examples and longer follow up.

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肥大型心筋症の早期心筋障害に対する BMIPP 心筋シンチと造影 MRI の比較研究

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【背景】線維性組織はガドリニウム造影 MRI において、遅延造影を示す。一方、心筋細胞の脂防酸代謝を画像化する BMIPP 心筋シンチグラムは、肥大型心筋症においても、BMIPP の集積低下が、しばしば認められることが報告され、肥大型心筋症（HCM）においても、脂防酸代謝障害が存在することを想定されている。HCM において、BMIPP 心筋シンチグラムで認められる代謝障害は、遅延造影 MRI で認められる線維化像で生じているばかりでなく、線維化に至る背景を形成していることが推定される。

今回は、HCM における BMIPP 心筋シンチグラムと遅延造影 MRI の所見を比較検討し、HCM の心筋細胞障害の進展およびその評価につき検討した。

【目的】HCM において、BMIPP スペクトおよび造影 MRI により検出される代謝異常と組織学的異常との関係を検討した。

【方法】1か月以内に BMIPP スペクトおよび造影 MRI を施行した 24人の HCM を対象とした。乳頭筋レベルの左室短軸像を 17分画し、それぞれの分画における、遅延造影と BMIPP の取り込み異常を比較検討した。

【結果】1）BMIPP 取り込み異常は、24例中 23例（95.8%）、408分画中 126分画に認められた（30.6%）。2）遅延造影は、24例中 18例（75%）、408分画中 50分画（12.2%）に認められた。3）（a）BMIPP 集積低下と遅延造影がともに陽性であったのは 24例中 19例（79.2%）に認めた。分画では、全408 分画中45分画（11.0%）であった。（b）BMIPP で集積低下かつ Gd-DTPA 達延造影は陰性であったのは 24例中 21例（87.5%）であった。分画では、全408 分画中80分画（19.6%）であった。（c）123I-BMIPP 集積低下陰性及び Gd-DTPA 達延造影陽性は 2例に認められた。分画では、全408 分画中5分画（1.3%）に認めた。（d）24例の HCM のうち、遅延造影、BMIPP 取り込み異常のいずれも認めなかった例は 1例のみであった（4.3%）。

【結論】BMIPP により検出される HCM の早期心筋代謝異常は、造影 MRI による遅延造影によって検出される器質的異常に比して、より早期に生じている可能性があり、BMIPP と造影 MRI による遅延造影の両者を行うことはHCM の病期を判定する上で有用であると考えられた。

＜キーワード＞肥大型心筋症、心臓 MRI、123I-BMIPP

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