Prognosis of hypertrophic cardiomyopathy: Assessment by $^{123}$I-BMIPP
($\beta$-methyl-p-$^{123}$Iiodophenyl pentadecanoic acid)
myocardial single photon emission computed tomography

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$^{123}$I-BMIPP ($\beta$-methyl-iodophenyl pentadecanoic acid) has shown unique properties for potential use in assessing myocardial metabolism. Previous basic and clinical studies demonstrated that the disturbances of myocardial metabolism precede the occurrence of myocardial perfusion abnormalities by using $^{201}$TI in hypertrophic myocardium. The present study was therefore undertaken to determine whether or not $^{123}$I-BMIPP myocardial SPECT is useful in predicting the prognosis of hypertrophic cardiomyopathy (HCM) in 65 patients in 6 facilities. There were 33 patients with non-obstructive HCM, 12 with obstructive HCM, 12 with apical HCM and 8 with dilated-phase HCM. Fasted patients at rest received an intravenous injection of 111 MBq of $^{123}$I-BMIPP. Twenty to thirty minutes later, myocardial SPECT was carried out. The BMIPP severity score (BMIPP SS) was evaluated semiquantitatively by using representative short axial SPECT images. We followed up the incidence of cardiac events for a mean period of 3.0 ± 0.6 years. Cardiac events occurred in 13 patients. Of these, 11 developed heart failure and 6 died (4 from heart failure and 2 from sudden death). The BMIPP SS in the dilated-phase HCM was significantly higher than that in the remaining HCM patients. The BMIPP SS for the survivors was significantly lower than that for the non-survivors. The BMIPP SS was particularly high in patients with fatal heart failure. Furthermore, there was a close negative correlation between the BMIPP SS and percent fractional shortening measured by echocardiography ($r = -0.49$). Finally, the mortality over the three years increased according to the extent of the BMIPP SS. In conclusion, these results indicate that the BMIPP SS is useful in evaluating the severity of HCM. We conclude that $^{123}$I-BMIPP is a valuable metabolic tracer in predicting the outcome of HCM.

Key words: myocardial metabolic imaging, $^{123}$I-BMIPP ($\beta$-methyl-iodophenyl pentadecanoic acid), hypertrophic cardiomyopathy, prognosis

INTRODUCTION

About 60–80% of myocardial energy metabolism is based on $\beta$-oxidation of free fatty acids. Assessment of myocardial fatty acid metabolism is therefore important not only in the pathophysiological clarification of ischemic or hypertrophic hearts, but also in assessing the therapeutic efficacy for these conditions. 1–3 The use of $^{14}$C-palmitate and positron emission tomography (PET) now makes it possible to obtain images of regional myocardial fatty acid metabolism. 4–6 The use of PET, however, has not spread widely and is limited to facilities that possess an in-house cyclotron. For this reason, the imaging of myocardial fatty acid metabolism by using various $^{123}$I-labeled fatty acids has been developed. 7–12 Representative
Table 1  The age, family history, electrocardiographic findings and echocardiographic findings for each group of hypertrophic cardiomyopathy

<table>
<thead>
<tr>
<th></th>
<th>Non-obstructive</th>
<th>Obstructive</th>
<th>Apical</th>
<th>Dilated-phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>33</td>
<td>12</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean</td>
<td>52 ± 16</td>
<td>54 ± 15</td>
<td>57 ± 7</td>
<td>56 ± 9</td>
</tr>
<tr>
<td>Range</td>
<td>21–79</td>
<td>27–81</td>
<td>44–68</td>
<td>43–66</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26 (78.8%)</td>
<td>7 (58.3%)</td>
<td>10 (83.3%)</td>
<td>3 (37.5%)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (21.2%)</td>
<td>5 (41.7%)</td>
<td>2 (16.7%)</td>
<td>5 (62.5%)</td>
</tr>
<tr>
<td>Family history of HCM</td>
<td>10 (30.3%)</td>
<td>3 (25.0%)</td>
<td>1 (8.3%)</td>
<td>2 (25.0%)</td>
</tr>
<tr>
<td>Electrocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Atrial fibrillation</td>
<td>6 (18.2%)</td>
<td>1 (8.3%)</td>
<td>1 (8.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>5 (15.2%)</td>
<td>2 (16.7%)</td>
<td>0</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Abnormal Q</td>
<td>12 (36.4%)</td>
<td>3 (25.0%)</td>
<td>1 (8.3%)</td>
<td>5 (62.5%)</td>
</tr>
<tr>
<td>Giant negative T</td>
<td>9 (27.3%)</td>
<td>3 (25.0%)</td>
<td>8 (8.3%)</td>
<td>0</td>
</tr>
<tr>
<td>SV1 + RV5</td>
<td>41.8 ± 20.8</td>
<td>40.2 ± 18.7</td>
<td>60.6 ± 13.4</td>
<td>36.8 ± 18.0</td>
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<tr>
<td>Echocardiography</td>
<td>(n = 33)</td>
<td>(n = 10)</td>
<td>(n = 11)</td>
<td>(n = 8)</td>
</tr>
<tr>
<td>IVSth (mm)</td>
<td>20.3 ± 4.6</td>
<td>21.2 ± 4.5</td>
<td>12.1 ± 1.8</td>
<td>16.9 ± 4.9</td>
</tr>
<tr>
<td>PWth (mm)</td>
<td>11.7 ± 2.9</td>
<td>14.0 ± 4.5</td>
<td>11.1 ± 1.8</td>
<td>11.3 ± 3.4</td>
</tr>
<tr>
<td>LVDd (mm)</td>
<td>43.3 ± 5.7</td>
<td>40.1 ± 5.4</td>
<td>48.5 ± 5.3</td>
<td>54.0 ± 13.0</td>
</tr>
<tr>
<td>LVDs (mm)</td>
<td>26.2 ± 5.7</td>
<td>22.5 ± 5.1</td>
<td>28.6 ± 3.3</td>
<td>41.3 ± 13.6</td>
</tr>
<tr>
<td>% FS</td>
<td>39.6 ± 7.8</td>
<td>44.6 ± 9.7</td>
<td>40.7 ± 6.6</td>
<td>24.6 ± 10.6</td>
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</tbody>
</table>

123I-labeled fatty acids used for such imaging are 123I-IPPA (iodophenyl pentadecanonic acid) and 123I-BMIPP (beta-methyl-iodophenyl pentadecanonic acid). The former is a straight-chain fatty acid. It is rapidly washed out of the myocardium.9,10 The latter is a branched-chain fatty acid, in which a methyl group has been introduced to the β-position of the carboxyl group. It highly accumulates in the myocardium, and is retained in the myocardium for long periods. Because of these features, the latter is suitable for imaging of myocardial fatty acid metabolism by single photon emission computed tomography (SPECT).11,12

Previous autoradiographic studies in spontaneously hypertensive rats and Bio146 Syrian hamsters with cardiomyopathy revealed that the regional distribution of 123I-BMIPP is discrepant from the myocardial perfusion assessed by using 201Tl in hypertrophic myocardium, and that disturbances of myocardial metabolism precede the occurrence of abnormalities of myocardial blood flow.13,14 Clinical results of hypertrophic cardiomyopathy, in which 123I-BMIPP was compared with 201Tl myocardial SPECT, revealed that the hypertrophic myocardium with a normal 201Tl distribution showed decreased 123I-BMIPP uptake, and that the reduction in cardiac function correlated with the extent of 123I-BMIPP defects.15-17 These previous findings suggest that regional disturbances of myocardial metabolism can be sensitively detected by imaging of myocardial fatty acid metabolism. The present study was therefore undertaken to examine whether or not 123I-BMIPP myocardial imaging is useful in the prognosis of hypertrophic cardiomyopathy in 65 patients with this disorder treated at 6 facilities.

METHODS

Patient selection
The subjects were 65 patients who were diagnosed as having hypertrophic cardiomyopathy (HCM) and in whom images of myocardial fatty acid metabolism were made by using 123I-BMIPP in 1990 and 1991 at the 6 facilities (Sapporo Medicine University; Hamamatsu University, School of Medicine; Kyoto Prefectural University of Medicine; Osaka University, Medical School; National Cardiovascular Center and Kurume University, School of Medicine). There were 46 males and 19 females, ranging in age from 21 to 81 years (mean; 53.7 ± 13.7 years). Depending on the type of HCM, 33 patients were signed to the non-obstructive HCM group, 12 to the obstructive HCM group, 12 to the apical HCM group, and 8 to the dilated-phase HCM group. Table 1 shows the age, sex, familial history, electrocardiographic findings and echocardiographic findings for each group.

Seventeen patients had complications (cerebral infarction in 1 case, diabetes mellitus in 4 cases and hypertension in 12 cases). Two patients had undergone pacemaker implantation. Drug therapy with beta-blockers had been administered to 18 patients (27.7%), calcium antagonist therapy to 41 (63.1%) and digitalis therapy to 6 (9.2%).

Definition of HCM
HCM was defined as the demonstration by echocardiography or left ventriculography, or at autopsy of asymmetrically hypertrophied, nondilated left ventricle in the absence of another cardiovascular or systemic disease.
that could produce left ventricular hypertrophy. Asymmetric septal hypertrophy was considered to be present if the end-diastolic thickness of the septum was at least 15 mm and its ratio to that of the left ventricular posterior wall was at least 1.3. The obstructive HCM was defined as systolic anterior motion of mitral valve leaflet detected by echocardiography and/or a pressure gradient greater than 30 mmHg in the left ventricle.\textsuperscript{14,19} If the echocardiographic apical long-axis or four-chamber view demonstrated apical hypertrophy and a characteristic spade-like configuration was demonstrated in the left ventriculograms, apical hypertrophy was considered to be present.\textsuperscript{21,22}

Dilated-phase HCM was defined as that phase representing an evolution from the typical asymmetrical hypertrophied and nondilated left ventricular wall thinning, cavity enlargement or impaired systolic function, or any combination of these abnormalities, and associated with clinical evidence of progressive congestive heart failure in the absence of hemodynamically significant coronary artery disease.\textsuperscript{23,24}

\textit{123I-BMIPP myocardial imaging and data analysis}

Fasted patients at rest received an intravenous injection of 111 MBq of \textit{123I-BMIPP} (Nihon Medi-Physics, Chiba, Japan). Twenty to thirty minutes later, myocardial SPECT was carried out in the supine position. On reconstructed short-axial views, 3 slices (a slice close to the apical region, a slice of the midventricular region and a slice close to the basal region) were selected. Each slice was divided into 8 segments (Fig. 1). The degree of \textit{123I-BMIPP} accumulation in each segment was visually graded on a 5-point scale: –1 (increased uptake), 0 (normal uptake), 1 (mildly decreased uptake), 2 (severely decreased uptake) and 3 (no uptake, i.e., defect). The grading was made jointly by 3 physicians who had more than 10 years experiences in nuclear cardiology, without knowledge of clinical data. The scores for all 24 segments in a given subject were totaled to yield the BMIPP severity score (BMIPP SS) for that subject.

\textit{Echocardiography}

Each subject underwent two-dimensional echocardiography at the time of \textit{123I-BMIPP} myocardial imaging. From the echocardiographic data, the interventricular septum thickness and the posterolateral wall thickness were determined. From the left ventricular end-diastolic dimension (LVDd) and the left ventricular end-systolic dimension (LVDs), the fractional shortening (\%FS) was calculated at each institution by using the following equation

\[
\%FS = \left(\frac{LVDd - LVDs}{LVDd}\right) \times 100
\]

The \%FS was regarded as an indicator of the severity of cardiac dysfunction, and was compared with the BMIPP SS. The calculation of each of these parameters was based on the standards prepared by the American Society of Echocardiography. The \%FS could not be calculated in 3 patients who did not undergo echocardiography. These 3 patients were excluded and 62 patients were evaluated.

\textit{Follow-up study}

For all subjects who underwent \textit{123I-BMIPP} myocardial imaging, we followed up the incidence of cardiac events from this end of the study to November, 1993. The mean follow-up period was 3.0 ± 0.6 years (range: 0.46–3.52 years). During the follow-up period, we examined: (1) the presence or absence of heart failure, (2) survival, and (3) cause (heart failures, arrhythmias or non-cardiac factors) of death and the date of death. The information sources were the medical chart for each patient and the report of the physician. All 62 patients were completely followed up.

\textit{Statistical analysis}

Data were expressed as the mean ± SD. The significance of differences in the score (BMIPP SS) between two groups was tested by Wilcoxon rank-sum test. The correlation between the \%FS and the BMIPP SS was evaluated on the basis of an analysis of the Spearman rank correlation coefficient. The Kaplan-Meier method was used to evaluate the cumulative survival curves. The significance of differences between two groups in survival curves was tested, by log-rank test. In all tests, \(p < 0.05\) was regarded as significant.

\textbf{RESULTS}

\textit{BMIPP severity score}

The mean BMIPP score for all segments (24 segments × 65 patients = 1560 segments) was 0.68 ± 0.94. The score was –1 for 14 segments, 0 for 866 segments, 1 for 388 segments, 2 for 188 segments and 3 for 104 segments, respectively. The BMIPP SS, as calculated from the total BMIPP score for individual patients, was 16.3 ± 13.1 (range: 0–54).

Figure 2 shows the BMIPP SS in each group. The BMIPP SS in the dilated-phase HCM group (38.1 ± 14.2) was significantly higher than that in the non-obstructive HCM group (15.3 ± 10.3; \(p = 0.006\)), the obstructive HCM group (13.0 ± 9.6; \(p = 0.0013\)) and the apical HCM group.
(7.9 ± 5.7; p = 0.0008). The BMIPP SS values for the obstructive and non-obstructive HCM groups were not significantly different. The BMIPP SS in the apical HCM group was slightly lower than those in the non-obstructive HCM group (p = 0.027), the obstructive HCM group (p = 0.18) and the dilated-phase HCM group (p = 0.0008).

There was no significant correlation between the BMIPP SS and age (r = 0.028, p = 0.83). The BMIPP SS was not correlated with any drug therapy. The BMIPP SS was not correlated with the existence of complications such as diabetic mellitus and hypertension.

**Relationship between the BMIPP SS and survival**

During the follow-up period, cardiac events occurred in 13 (21.0%) of the 62 patients. That is, 11 patients (17.7%) developed heart failure (leading to death in 4), and 6 patients (9.7%) died of cardiac disease (4 deaths from heart failure and 2 from arrhythmias). There were no deaths from non-cardiac factors.

The mean age of the 4 patients who died of heart failure (1 male and 3 females) was 55.5 ± 5.8 years (range: 48–61 years). Of the 2 patients who died of arrhythmias, one was a 27-year-old female and the other was a 53-year-old male.

Figure 3 shows the BMIPP SS for the survivors (n = 56) and those who died (n = 6). The BMIPP SS for the non-survivors (36.7 ± 16.7) was significantly (p = 0.0027) higher than that for the survivors (13.7 ± 9.9). The BMIPP SS was particularly high in the 4 patients who died of heart failure (mean, 45.5 ± 9.3; range, 34 to 54), but it was relatively low in the 2 patients who died of arrhythmias (9 and 29, respectively).

Although the BMIPP SS for the survivors was significantly lower than that for the non-survivors (p = 0.0027), as mentioned above, the score was slightly high in survivors in whom HCM was complicated by heart failure.

**Annals of Nuclear Medicine**
failure; n = 4) and the fatal arrhythmia group (the group of patients who died of arrhythmias; n = 2). The BMIPP SS in the cardiac event free group (12.6 ± 8.4) was lower than that in the heart failure group (23.1 ± 14.3), although this difference was not significant (p = 0.059). The BMIPP SS for the cardiac event free group did not differ significantly from that for the death (arrhythmia) group (19.0 ± 14.1) (p = 0.38), but it was significantly lower than that for the fatal heart failure group (45.5 ± 9.3) (p = 0.001). The BMIPP SS in the heart failure group (23.1 ± 14.3) was significantly lower than that in the fatal heart failure group (45.5 ± 9.3) (p = 0.029), although it did not differ significantly from that in the cardiac event free group (p = 0.059) or the sudden death group (p = 0.88).

**Relationship between BMIPP SS and echocardiographic findings**

Figure 6 shows the relationship between the %FS, as calculated from echocardiograms, and the BMIPP SS for each subject. The average %FS was 40.4 ± 8.0% (range: 20 to 58%) in the cardiac event free group (n = 47), 36.4 ± 6.4% (range: 28 to 45) in the heart failure group (n = 5), 16.5 ± 3.7% (range: 13 to 21%) in the fatal heart failure group (n = 4), and 42.0 ± 11.3% (range: 34 and 50) in the sudden death group (n = 2).

There was a close negative correlation between the BMIPP SS and %FS (r = −0.49, p < 0.001). As the cardiac function decreased, the BMIPP SS increased. No cardiac events occurred in any of the 4 patients in whom both %FS and BMIPP SS were below 30. Of the 6 patients in whom %FS was below 30 and BMIPP SS was over 30, 5 (83.3%) had cardiac events. Of these 5 patients, 4 died of heart failure and the remaining patient developed heart failure. The incidence of cardiac events was therefore high when an increase in the BMIPP SS accompanied low cardiac function (%FS). Of 48 patients in whom %FS was over 30, only 3 (6.3%) had a BMIPP SS higher than 30. Of these 3 patients, 2 developed heart failure. Of 45 patients in whom the BMIPP SS was below 30, 2 developed heart failure and another 2 died of arrhythmias.

**Relationship between the BMIPP SS and mortality**

Of the 62 patients, 8.1% died during the three-year period. Figure 7 shows the cumulative survival curve (Kaplan-Meier method) for the six groups of patients divided by the BMIPP SS Group I (score 0–9; n = 27), Group II (10–19; n = 18), Group III (20–29; n = 10), Group IV (30–39; n = 5), Group V (40–49; n = 3) and Group VI (50 and over; n = 2). The mortality over the three years increased slightly with the BMIPP SS (3.7% for Group I, 0.0% for Group II, 10.0% for Group III, 20.0% for Group IV, 33.3% for Group V and 100% for Group VI, respectively).
DISCUSSION

1. Natural history of hypertrophic cardiomyopathy
In most cases of hypertrophic cardiomyopathy, cardiac contractility is preserved relatively well. The five- to ten-year survival rates for patients with this disease have been reported to be 80–90%, but the incidence of sudden death or cardiac events is high for patients with this disease under 30 years of age. It has also been reported that patients with familial HCM tended to develop heart failure and rapid exacerbation of the condition. We encountered cases of familial HCM in which thallium perfusion was abnormal, cardiomegaly progressed, cardiac function was reduced, and serum enzymes derived from the myocardium such as CPK-MB and LDH 1 increased. Myocardial biopsy demonstrated myocardial fiber disarray with fibrosis. We termed this type as “dilated-phase HCM.” These cases showed diffuse, positive accumulation of 111In-antimyosin Fab in the myocardium, suggesting the presence of necrosis. Similar to our finding, Maron et al. reported that the coexistence of sudden cardiac death and end-stage heart failure was sometimes noted in cases of familial HCM, and suggested that such cases are more common than previously estimated.

HCM is therefore a primary cardiac disease and has broad morphologic and clinical spectra. As a possible explanation for the diverse pathophysiological features of HCM, a relationship between myocardial hypertrophy and myocardial degeneration has been suggested. Furthermore, since some HCM patients with normal coronary arteries sometimes develop angina or thallium perfusion defects, the involvement of small coronary artery disease in HCM has been suggested. In this connection, several investigators reported that transient perfusion defects were noted in about half of HCM patients when examined by means of exercise 201Tl myocardial scintigraphy. O’Gara reported that 201Tl myocardial SPECT revealed defects in 41 (57%) of 72 patients with HCM, and that LVEF was below 50% in 4 of 17 patients with persistent perfusion defects, in contrast to the 24 patients with transient perfusion defects in whom LVEF was normal. These results demonstrate the involvement of myocardial ischemia and/or scar in HCM. These findings indicated that prognosis of hypertrophic cardiomyopathy is chiefly determined not only by arrhythmias (e.g., atrial fibrillation and ventricular tachycardia) which can cause sudden death, but also by the development of heart failure. Early detection of heart failure in HCM is therefore essential.

2. 123I-BMIPP myocardial imaging and severity of HCM
Glucose analogs for single-photon imaging are not yet available, but some radiiodinated fatty acids can serve as metabolic tracers. In cardiomyopathy, β-oxidation of free fatty acid, which accounts for 60–80% of myocardial energy metabolism under anaerobic conditions, is inhibited. In consideration of routine examinations primarily dependent on SPECT, radiiodinated free fatty acid is therefore suitable for imaging myocardial metabolism. Of these agents, 123I-BMIPP is superior for myocardial SPECT imaging, because of its higher uptake and prolonged retention in the myocardium. In animal experiments with spontaneous hypertensive rats and Bio 14.6 Syrian hamsters, 123I-BMIPP uptake was reduced before the occurrence of abnormalities in myocardial blood flow distribution. In some cardiomyopathies, myocardial metabolism is impaired earlier than myocardial perfusion, because ATP production is reduced by damage to the myocardial cell membrane, and mitochondrial dysfunction.

A phase III clinical trial of 123I-BMIPP was recently completed in Japan. Interestingly, decreased 123I-BMIPP uptake was observed in 56 of 70 (80%) patients with HCM in this trial. Kurata et al. performed 123I-BMIPP and thallium myocardial SPECT in 17 HCM patients, and observed that uptake of 123I-BMIPP was noticeably reduced in 10 patients who showed signs of severe asymmetric hypertrophy. Moreover, 123I-BMIPP uptake was reduced at sites that corresponded to hypertrophied areas where thallium uptake was increased.

In the present study, the BMIPP SS varied among different types of hypertrophic cardiomyopathy. It was particularly high in the dilated-phase HCM group and low in the apical HCM group, although it was not significantly different in obstructive and non-obstructive HCM. As shown in Figure 6, a significant correlation was noted between the BMIPP SS and the %FS as determined by echocardiography. These results indicate that myocardial SPECT with 123I-BMIPP is very useful in evaluating the severity of HCM.

3. 123I-BMIPP myocardial imaging and prognosis of HCM
Following the finding that 123I-BMIPP myocardial SPECT is more useful than 201Tl myocardial SPECT in the early detection of HCM and that it permits the evaluation of the severity of HCM, we examined the utility of the BMIPP SS as a predictor of prognosis in HCM. The BMIPP SS was high in HCM patients who died or developed heart failure. The three-year survival curves, according to the Kaplan-Meier method, revealed that the prognosis became poorer as the BMIPP SS increased. Prior to the present study, some investigators reported prediction of the outcome of HCM on the basis of clinical signs, arrhythmias and echocardiographic findings. To the best of our knowledge, no previous studies used myocardial metabolic imaging to establish the prognosis of HCM. We conclude that the present study is valuable in that it demonstrated the high utility of metabolic imaging with SPECT in predicting the outcome of HCM, on the basis of the data collected from a large number of HCM patients.
REFERENCES


