

# Impairment of BMIPP Accumulation at Junction of Ventricular Septum and Left and Right Ventricular Free Walls in Hypertrophic Cardiomyopathy

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Myocardial scintigraphy using  $^{123}\text{I}$ -15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) reveals a high incidence of reduced accumulation of the tracer in patients with hypertrophic cardiomyopathy (HCM). This defect is thought to reflect impairment of myocardial fatty acid metabolism. In this study, the distribution of BMIPP defects was characterized and correlated with the clinical features of patients with HCM. **Methods:** Thirty patients with asymmetric septal hypertrophy (ASH) were examined. Regional BMIPP accumulation was evaluated. Each region was normalized to the accumulation in the nonhypertrophic lateral region, which was represented as 100% on each bull's-eye map. The corresponding thallium accumulation for each region was then used to correct for the partial-volume effect. **Results:** BMIPP accumulation was significantly less in the septal portion of the anterior wall (As), the septal portion of the posterior wall (Ps) and the apex than in the lateral segments. BMIPP defects were significantly more frequent in the As, Ps and apical segments (20.0%, 20.0% and 33.3%, respectively) and were present in the As or Ps segments in 8 patients (27%). The patients with BMIPP defects in the As or Ps segments had a more frequent family history of HCM or sudden death and severe cardiac dysfunction. **Conclusion:** BMIPP defects occur predominantly in the As and Ps segments in some patients with ASH, which is often associated with severe cardiac dysfunction. The distribution of BMIPP defects may contribute to the classification of HCM and the assessment of its severity.

**Key Words:**  $^{123}\text{I}$ -15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid; fatty acid metabolism; hypertrophic cardiomyopathy

**J Nucl Med 1999; 40:2007–2013**

Iodine-123-labeled 15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) (1–3) is a branched fatty acid with a prolonged retention time in the myocardium (4,5). A small percentage of BMIPP is metabolized through initial  $\alpha$ - and  $\beta$ -oxidation, followed by catabolic washout (6,7). BMIPP is, therefore, considered to be suitable for assessing myocardial

fatty acid metabolism by SPECT because the washout of BMIPP is slow enough to be negligible in the SPECT protocol (6). An increasing number of studies of hypertrophic cardiomyopathy (HCM) have been performed using BMIPP and have shown inhomogeneous accumulation of BMIPP and a discrepancy in distribution between BMIPP and the perfusion tracer (8–15). However, limited data have been available on the precise assessment of BMIPP distribution (13,15) and the relationship between BMIPP defects and clinical features (9,16). Thus, this study focused on the sites of BMIPP defects and correlated the characteristics of BMIPP defects with clinical findings.

## MATERIALS AND METHODS

### Study Patients

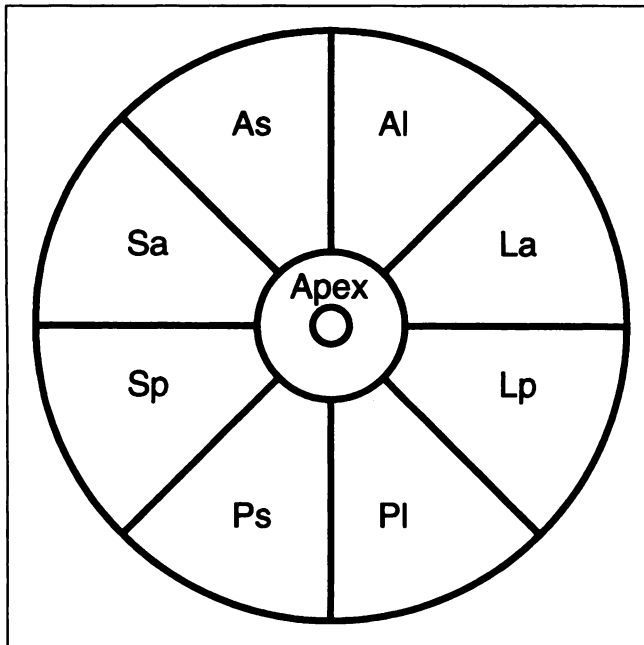
The study group comprised 30 patients with HCM accompanied by asymmetric septal hypertrophy (ASH) (23 men, 7 women; age range 24–69 y; mean age 51 y). The diagnosis of HCM was based on the clinical and electrocardiographic findings and echocardiographic demonstration of a hypertrophied left ventricle in the absence of any other cardiac or systemic disease that itself might produce left ventricular hypertrophy (17–19). All patients had normal coronary angiography findings. ASH was considered to be present if the end-diastolic thickness of the ventricular septum was at least 13 mm and its ratio to the thickness of the left ventricular posterior wall was at least 1.3. The average end-diastolic thicknesses of the ventricular septum and the posterior wall were  $20 \pm 4$  and  $11 \pm 2$  mm, respectively. The ratio of the ventricular septum thickness to the posterior wall thickness was  $1.8 \pm 0.4$ . To elucidate the relationship between the sites of hypertrophied myocardium and the sites of BMIPP defects, the patients were limited to those with involvement of the anterior ventricular septum alone or both the anterior and the posterior ventricular septa (types 1 and 2, respectively, of Maron et al. [20]). No patients with a pressure gradient of the left ventricular outflow were included. All medications that might affect myocardial perfusion or metabolism were withdrawn at least 48 h before the study. Informed consent was obtained from all patients, and the study protocol was approved by the research committee of the institution.

### Protocol

SPECT imaging was started 20 min after administration of 111 MBq (3 mCi) BMIPP with the patients at rest after overnight

Received Nov. 24, 1998; revision accepted Apr. 9, 1999.

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**FIGURE 1.** Schema of nine regions on bull's-eye map. Al = anterior wall, lateral portion; As = anterior wall, septal portion; La = lateral wall, anterior portion; Lp = lateral wall, posterior portion; Pl = posterior wall, lateral portion; Ps = posterior wall, septal portion; Sa = septum, anterior portion; Sp = septum, posterior portion.

fasting. Data were obtained using a rotating digital scintillation camera (901A; Toshiba Co., Tokyo, Japan) equipped with a collimator dedicated to  $^{123}\text{I}$  on the 159-keV photopeak with a 20% window; 32 projections (30 s per projection) were collected over  $180^\circ$  from the  $45^\circ$  left posterior oblique position to the  $45^\circ$  right anterior oblique position. Data were recorded in a  $64 \times 64$  matrix on a dedicated nuclear medicine computer system (GMS550U; Toshiba). Myocardial tomograms were reconstructed using a Shepp-Logan filter. No attenuation or scatter correction was performed. Thallium imaging was performed within 1 mo of BMIPP imaging using the same data acquisition technique with the

following exceptions: SPECT imaging was started 10 min after injection; the data acquisition time per projection was 40 s; and a low-energy, high-resolution collimator on the 70-keV photopeak with a 20% window was used.

Two patients were followed up with BMIPP and thallium myocardial scintigraphy to observe serial changes in the distribution of tracer defects.

### Quantitative Image Analysis

For quantitative analysis of tracer accumulation, a circumferential profile curve was generated from apical to basal short-axis slices to create a bull's-eye map (21). The bull's-eye map was divided into nine segments: Al (anterior wall, lateral portion), As (anterior wall, septal portion), La (lateral wall, anterior portion), Lp (lateral wall, posterior portion), Pl (posterior wall, lateral portion), Ps (posterior wall, septal portion), Sa (septum, anterior portion), Sp (septum, posterior portion) and apex (Fig. 1). A study using PET found that myocardial blood flow at rest, after correction for a partial-volume effect, was approximately homogeneous throughout the myocardium (22). Therefore, the regional BMIPP accumulation (mean count per pixel) was corrected for a partial-volume effect using the regional thallium accumulation (mean count per pixel) in a manner similar to that described by others (14). The BMIPP and thallium accumulation was defined as 100% in the nonhypertrophic La or Lp segments with higher accumulation, which was used as the standard to normalize the percentage of regional accumulation of each tracer. The percentage of regional BMIPP accumulation corrected for the partial-volume effect was calculated using the following equation: Corrected percentage of regional BMIPP accumulation = (normalized percentage of regional BMIPP accumulation/normalized percentage of regional thallium accumulation)  $\times$  100. The incidence of reduction of the BMIPP, thallium and corrected BMIPP accumulation was analyzed for each segment. The accumulation was considered to be defective when the percentage of accumulation was lower than the mean value minus two SDs in the La segment (Tables 1–3).

### Statistical Analysis

The data are presented as mean  $\pm$  SD. Parameters were compared by one-way analysis of variance with a post hoc Scheffé F test or an unpaired *t* test. A  $\chi^2$  test or Fisher exact test was used as

**TABLE 1**  
Percentage Regional BMIPP Accumulation in Patients with Hypertrophic Cardiomyopathy

	Region									P
	Al	As	Sa	Sp	Ps	Pl	Lp	La	Apex	
BMIPP accumulation* (%)	81.3 $\pm$ 8.8	75.8 $\pm$ 10.9†	80.7 $\pm$ 11.9	81.2 $\pm$ 13.5	73.3 $\pm$ 12.4‡	78.0 $\pm$ 6.5	86.3 $\pm$ 5.7	87.2 $\pm$ 5.7	69.3 $\pm$ 8.9§	<0.0001
Reduced accumulation (%)	10.0	36.7	26.7	23.3	36.7	43.3	3.3	6.7	76.7	

\*Mean  $\pm$  SD.

†*P* < 0.05 vs. Lp, *P* < 0.02 vs. La.

‡*P* < 0.01 vs. Lp, *P* < 0.001 vs. La.

§*P* < 0.01 vs. Al and Sp, *P* < 0.02 vs. Sa, *P* < 0.0001 vs. Lp and La.

BMIPP =  $^{123}\text{I}$ -15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid; Al = anterior wall, lateral portion; As = anterior wall, septal portion; Sa = septum, anterior portion; Sp = septum, posterior portion; Ps = posterior wall, septal portion; Pl = posterior wall, lateral portion; Lp = lateral wall, posterior portion; La = lateral wall, anterior portion.

**TABLE 2**  
Percentage Regional Thallium Accumulation in Patients with Hypertrophic Cardiomyopathy

	Region									P
	Al	As	Sa	Sp	Ps	Pl	Lp	La	Apex	
Thallium accumulation* (%)	86.4 ± 5.4	83.9 ± 11.8	85.1 ± 11.2	83.9 ± 10.7	77.8 ± 10.5	80.0 ± 7.7	85.9 ± 6.9	86.9 ± 5.1	73.9 ± 7.7†	<0.0001
Reduced accumulation (%)	6.7	23.3	13.3	10.0	46.7	36.7	20.0	6.7	70.0	

\*Mean ± SD.

†P < 0.001 versus Al, Lp and La; P < 0.02 versus As and Sp; P < 0.01 versus Sa.

Al = anterior wall, lateral portion; As = anterior wall, septal portion; Sa = septum, anterior portion; Sp = septum, posterior portion; Ps = posterior wall, septal portion; Pl = posterior wall, lateral portion; Lp = lateral wall, posterior portion; La = lateral wall, anterior portion.

appropriate to compare differences in the proportion of the number of patients between two groups. P < 0.05 was considered statistically significant.

## RESULTS

### BMIPP, Thallium and Corrected BMIPP Accumulation

The mean regional BMIPP accumulation was significantly less in As, Ps and apical segments (Table 1). The incidence of BMIPP defects tended to be high in As segments (36.7%), Ps segments (36.7%), Pl segments (43.3%) and apical segments (76.7%).

The mean regional thallium accumulation was significantly less in only the apex (Table 2). The incidence of thallium defects tended to be high in As segments (23.3%), Ps segments (46.7%) and Pl segments (36.7%) and was markedly high in apical segments (70.0%).

The mean corrected BMIPP accumulation was significantly less in the As, Ps and apical segments than in the lateral segments (Table 3). BMIPP defects were significantly

more frequent in As segments (20.0%), Ps segments (20.0%) and apical segments (33.3%). After the correction, no segments showed BMIPP defects in the lateral wall; furthermore, the incidence of BMIPP defects in the Pl segments decreased markedly from 43.3% to 3.3%. BMIPP was defective in the As or Ps segments in 8 patients (27%). Figure 2 presents representative tomograms showing marked BMIPP defects in the regions corresponding approximately to As, Ps and apical segments.

### Characteristics of Patients with BMIPP Defects in As and Ps Segments

The As and Ps segments correspond, respectively, to the anterior and posterior junctions between the ventricular septum and the left and right ventricular free walls. Accordingly, the expression "junctional type" was used for the 8 patients with a corrected BMIPP defect in the As or Ps segments but without BMIPP defects in either the Sa or the Sp segments, and the expression "nonjunctional type" was

**TABLE 3**  
Corrected Percentage of Regional BMIPP Accumulation in Patients with Hypertrophic Cardiomyopathy

	Region									P
	Al	As	Sa	Sp	Ps	Pl	Lp	La	Apex	
Corrected BMIPP accumulation* (%)	95.4 ± 6.9	90.8 ± 7.9†	95.0 ± 7.8	96.8 ± 10.5	91.2 ± 10.1‡	98.7 ± 9.4	101.0 ± 9.7	100.6 ± 8.2	90.9 ± 10.1§	<0.0001
Reduced accumulation (%)	3.3	20.0	6.7	10.0	20.0	3.3	0	0	33.3	

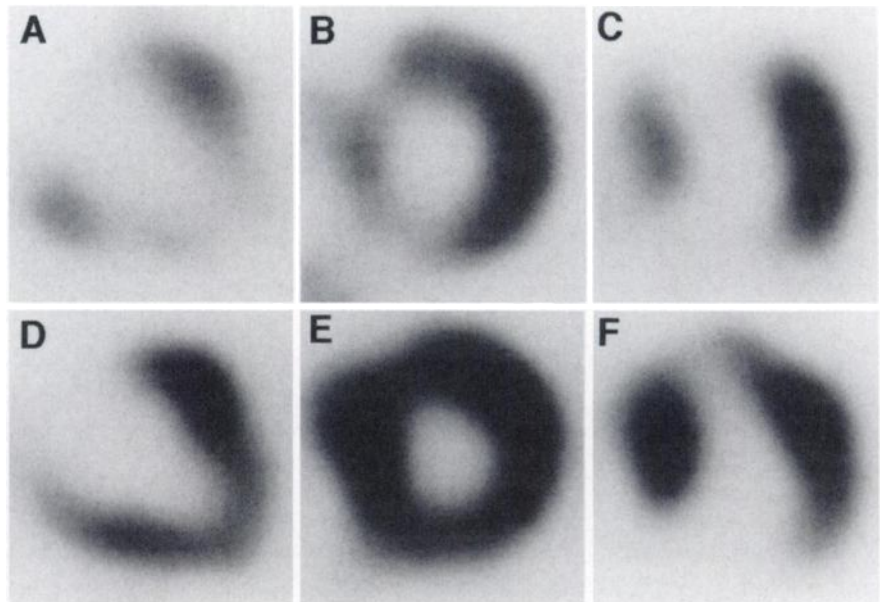
\*Mean ± SD.

†P < 0.05 vs. La, P < 0.02 vs. Lp.

‡P < 0.05 vs. La and Lp.

§P < 0.05 vs. Lp.

BMIPP = <sup>123</sup>I-15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid; Al = anterior wall, lateral portion; As = anterior wall, septal portion; Sa = septum, anterior portion; Sp, septum, posterior portion; Ps = posterior wall, septal portion; Pl = posterior wall, lateral portion; Lp = lateral wall, posterior portion; La = lateral wall, anterior portion.



**FIGURE 2.** BMIPP (top) and thallium (bottom) studies along vertical long axis (A and D), short axis (B and E) and horizontal long axis (C and F). BMIPP defect is severe in As, Ps and apical segments, but thallium defect is not. Heart seems to rotate slightly counterclockwise, judging from site of junction of ventricular septum and right ventricular free wall.

used for the other 22 patients. The junctional-type patients included 4 with a corrected BMIPP defect in both the As and the Ps segments, 2 with a corrected BMIPP defect in the As segments alone and 2 with a corrected BMIPP defect in the Ps segments alone. No patients had marked BMIPP defects in all As, Sa, Sp and Ps segments.

The age at diagnosis and the sex were not significantly different between the two types, but a family history of HCM or sudden death was significantly more frequent in the junctional type ( $P < 0.05$ ). The junctional type was found to include significantly more patients with severe dysfunction (i.e., New York Heart Association functional class 3) than did the nonjunctional type ( $P < 0.001$ ).

Furthermore, the incidence of corrected BMIPP defect was significantly higher in the junctional type (32% of 72 segments) than in the nonjunctional type (3% of 198 segments) ( $P < 0.0001$ ).

Echocardiographically, the junctional-type patients had a significantly thinner ventricular septum ( $P < 0.02$ ), a lower ratio of the ventricular septal thickness to the posterior wall thickness ( $P < 0.05$ ), a lower fractional shortening (FS) of the left ventricular dimension ( $P < 0.0001$ ) and significantly higher end-diastolic and end-systolic dimensions ( $P < 0.01$  and  $P = 0.0001$ , respectively) (Table 4).

#### Temporal Changes in BMIPP and Thallium Myocardial Scintigrams

Figure 3 presents the bull's-eye maps of BMIPP and thallium in a patient who was followed up for 42 mo. The first examination revealed BMIPP defects in the As, Ps and apical segments, whereas a thallium defect was noted in only a narrow region near the apex. However, 30- and 42-mo follow-up examinations showed gradual expansion of the region of BMIPP defects to include the ventricular septum and the anterior and posterior left ventricular free walls. The region of thallium defects also expanded from the apex to

include the As and Ps segments. However, the area of thallium defects was more limited than was the area of BMIPP defects at each examination.

Echocardiography performed within 1 mo of the first

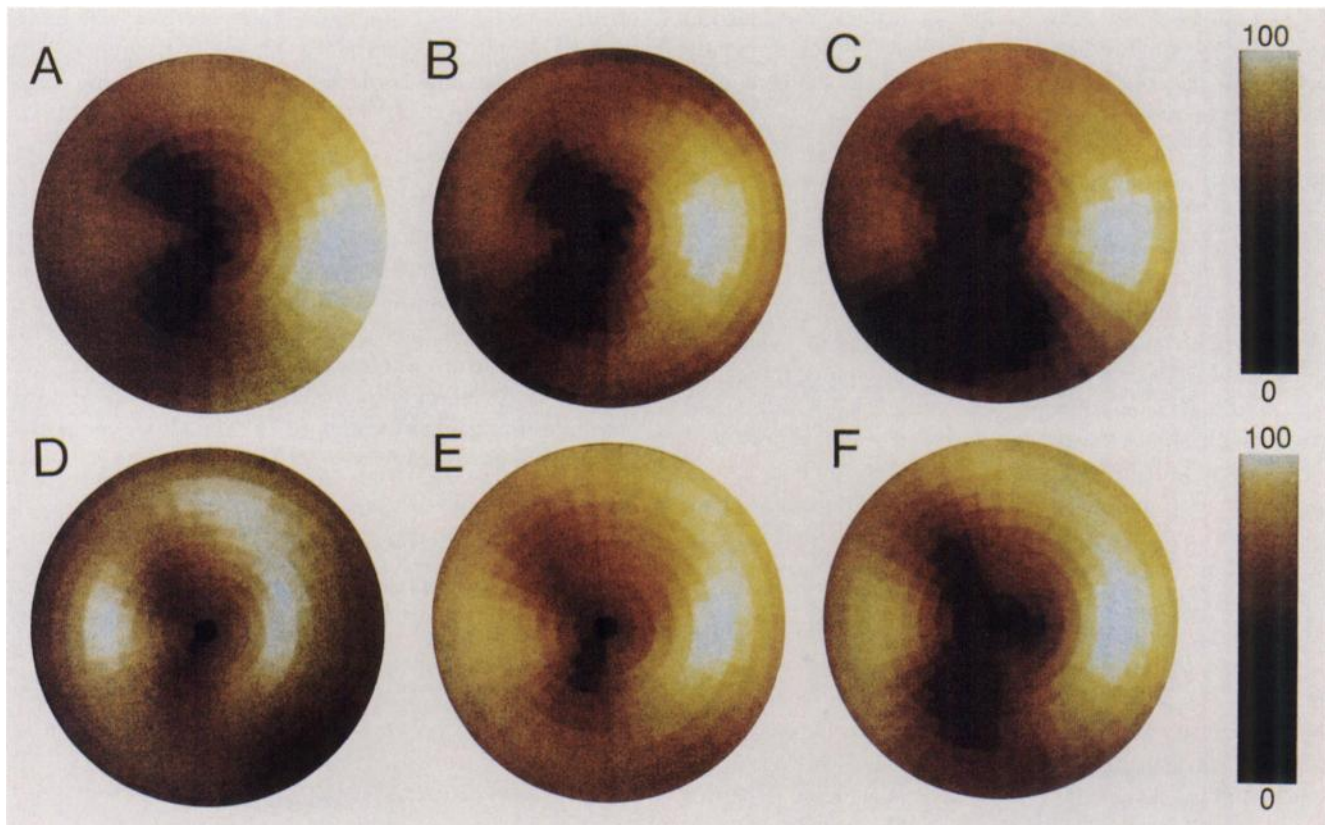
**TABLE 4**

Clinical, Scintigraphic and Echocardiographic Findings for Junctional and Nonjunctional Hypertrophic Cardiomyopathy

	Junctional	Nonjunctional	<i>P</i>
<b>Clinical characteristics</b>			
No. of patients	8 (27%)	22 (73%)	
Age at diagnosis* (y)	48 ± 10	43 ± 14	NS
No. of men	4 (50%)	19 (86%)	NS
Family history of HCM or sudden death	6 (75%)	7 (32%)	<0.05
<b>Cardiac functional capacity (NYHA functional class)</b>			
1	1 (13%)	14 (64%)	
2	2 (25%)	8 (36%)	<0.001
3	5 (63%)	0 (0%)	
<b>Scintigraphic findings</b>			
Segments with reduction of corrected BMIPP accumulation	23/72 (32%)	6/198 (3%)	<0.0001
<b>Echocardiographic findings of left ventricle*</b>			
VST (mm)	17 ± 4	21 ± 4	<0.02
PWT (mm)	11 ± 3	11 ± 2	NS
VST/PWT ratio	1.6 ± 0.4	1.9 ± 0.3	<0.05
Diastolic dimension (mm)	56 ± 10	47 ± 6	<0.01
Systolic dimension (mm)	42 ± 12	28 ± 6	0.0001
Fractional shortening (%)	26 ± 11	42 ± 7	<0.0001

NS = not significant; HCM = hypertrophic cardiomyopathy; NYHA = New York Heart Association; BMIPP = <sup>123</sup>I-15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid; VST = ventricular septal thickness; PWT = posterior wall thickness.

\*Mean ± SD.



**FIGURE 3.** Bull's-eye maps of BMIPP (top) and thallium (bottom) during first examination (A and D), second examination (30 mo after first) (B and E) and third examination (12 mo after second) (C and F). (A) BMIPP accumulation is clearly reduced in As, Ps and apical segments. (D) Thallium defect is in very limited region near apex. (B and C) BMIPP defect expands to neighboring portions. (E) Thallium defect is in only narrow apical area. (F) Thallium defect is also in As and Ps segments.

SPECT examination showed that the FS of the left ventricular dimension was 38%. This value decreased to 30% and 26% at 30 and 42 mo, respectively. This decrease suggests a progression of the patient's cardiac dysfunction. At the time of the first set of examinations, the patient complained of dyspnea, palpitation and other such symptoms when subjected to severe exercise, but 30 mo later she complained of these same symptoms even with light exercise. Although the symptoms had worsened by the time of the last set of examinations, no coronary stenosis was found during cardiac catheterization. The bull's-eye maps of the other patient, who was followed up for 21 mo, showed a similar pattern of expansion of defects, with an FS reduction from 42% to 36%.

## DISCUSSION

The reduction of BMIPP accumulation was most marked and frequently observed in the As, Ps and apical segments, which usually are not the predominant sites of hypertrophy in patients with HCM classified as types 1 and 2 of Maron et al. (20). A similar tendency was observed for thallium accumulation, although to a lesser extent. Significantly more patients with BMIPP defects in the As or Ps segments had a family history of HCM or sudden death and severe cardiac

dysfunction. Therefore, evaluation of BMIPP defects may be useful for classifying HCM and assessing its severity.

In the patient shown in Figure 3, BMIPP defects expanded from the As and Ps segments to encompass the hypertrophied ventricular septum. This process may be common to some patients with HCM. The expansion of tracer defects over time may be related to aggravation of cardiac dysfunction. Because the expansion was observed earlier with BMIPP than with thallium, the BMIPP defects may have preceded the thallium defects in other patients as well.

Because the patients in this study had ASH, a partial-volume effect may have led to underestimation of tracer accumulation. However, the As and Ps segments were not the sites of minimal thickness; thickness was usually minimal in the lateral wall. Therefore, the tracer defects may be assessed safely without excessive underestimation by comparing raw data with tracer accumulation in the lateral wall. Tissue attenuation may affect the homogeneity of SPECT images. However, neither women with well-developed breasts nor persons weighing more than 73 kg or having a body mass index greater than 25 were included in this study. Therefore, ignorance of the effect of tissue attenuation may not be greatly responsible for the inhomogeneity. Kinetic blurring seems to be unavoidable when images are recorded

by nongated SPECT. However, the contribution of blurring to image inhomogeneity may not have differed greatly among the patients because the images were obtained under the same condition, i.e., at rest.

Regional BMIPP accumulation was tentatively corrected for the partial-volume effect using the thallium accumulation in the corresponding region (14,22). With this correction, the extent and incidence of BMIPP defects decreased considerably, especially in the PI segments. In the La and Lp segments, no BMIPP defects were found after the correction. BMIPP defects in the As and Ps segments were not considered to be caused by only a partial-volume effect and impaired perfusion. However, energy levels of tracers and patients' physiques may possibly influence attenuation.

The predominant site of BMIPP defects found in this study differs from those (ventricular septum [8], antero-septal region [12] and hypertrophied portion [14]) found in other studies. This disagreement may be associated, in part, with the many etiologies and varied clinical features of HCM. Furthermore, in the other studies, the BMIPP accumulation in hypertrophied regions was compared with that in nonhypertrophied regions; hence, halfway areas such as the As and Ps segments, which usually are adjacent to hypertrophied regions, may not have received attention. However, about half of the segments with BMIPP defects were not hypertrophied in HCM (11). BMIPP accumulation was significantly lower than thallium accumulation in about half of the anterior, inferior and septal segments (9). The ratio of BMIPP accumulation to thallium accumulation was lower in the antero-septal, infero-septal, apical and septal regions, the former two being quite close to the As and Ps segments (15).

Kuribayashi and Roberts (23) reported that, in autopsied hearts with HCM, abnormalities of myocardial architecture—i.e., myocardial fascicular disarray, fibrosis and tissue clefts—were most severe in the anterior and posterior junctions between the ventricular septum and the left and right ventricular free walls, which approximately correspond to the As and Ps segments, respectively. Kuribayashi and Roberts did not examine the apical portion. In the portions of the ventricular septum and the left and right ventricular free walls adjacent to the junctions, myocardial fiber disarray and milder fibrosis were present. In contrast, myocardial architecture was always almost normal in the lateral portions of the left ventricular free walls. Thus, compared with the pathologic findings, the segments with the most severe impairment of BMIPP accumulation correspond to the anterior and posterior junctions, and a milder BMIPP defect may have occurred in the portions adjacent to the junctions.

The mechanism by which tracer accumulation is impaired in HCM remains to be clarified. Histologic abnormality in the myocardium may correlate with tracer defects. The cell membrane and organelle of myocytes are unlikely to stay intact and function normally under abnormal histologic conditions, disturbing the uptake and retention of BMIPP and thallium and the intracellular metabolism of BMIPP (24,25). This possibility may reduce the validity of the

correction method for the partial-volume effect. The intact histology of the left ventricular lateral wall supports the validity of assessing BMIPP defects by comparing them with this segment.

## CONCLUSION

The results indicate that, in some patients with ASH, BMIPP defects are most marked and frequently observed in the anterior and posterior junctions between the ventricular septum and the left and right ventricular free walls. This pattern of impairment is often associated with severe cardiac dysfunction. Accordingly, evaluation of BMIPP defects contributes to the classification of HCM and may be useful for assessing its severity.

## ACKNOWLEDGMENTS

This study was supported by research grant 8A-5 for cardiovascular disease from the Ministry of Health and Welfare of Japan.

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