

# Association of Iodine-123 BMIPP and MIBG Cardiac Uptakes with Left Ventricular Functional Parameters Assessed by Gated Myocardial Perfusion SPECT

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**Abstract-** We investigated how the degree of cardiac uptakes of radioactive fatty acid (FA) analog (<sup>123</sup>I-BMIPP) or norepinephrine (NE) analog (<sup>123</sup>I-MIBG) was related to left ventricular (LV) functional parameters in patients with heart disease, which might be a predictor of cardiac events.

Patients with ejection fraction (EF) of 16.2%-82.2% underwent <sup>123</sup>I-BMIPP or <sup>123</sup>I-MIBG myocardial scintigraphy, and were followed up over 1177±486 days. LV systolic functional parameter EF, diastolic parameters 1/3FR (first third filling rate), PFR (peak filling rate), and TPF (time to PFR) were calculated using quantitative gated SPECT.

<sup>123</sup>I-BMIPP uptake (n=30) was significantly correlated with EF, 1/3FR, and PFR but not TPF. <sup>123</sup>I-MIBG uptake (n=37) was also correlated with EF, 1/3FR, and PFR but not TPF. In contrast, TPF was positively correlated with age, and was significantly longer in women than in men. Such findings were also observed in normal EF patients (≥50%, n=100). Kaplan–Meier analysis showed the occurrence of earlier cardiac events in the case of patients with decreased <sup>123</sup>I-BMIPP and <sup>123</sup>I-MIBG uptake, decreased PFR, and prolonged TPF.

The degree of decreased cardiac uptakes of FA and NE may be associated with the grade of systolic and diastolic dysfunctions assessed by EF, PFR, and 1/3FR. In contrast, prolonged TPF, another diastolic parameter, may rather be caused by aging and female gender, independent of EF. Despite these differences, myocardial FA metabolism impairment, cardiac sympathetic nerve inactivity, decreased PFR, and prolonged TPF may all indicate poor cardiac prognosis in patients with heart disease.

**Keywords-** <sup>123</sup>I-BMIPP; <sup>123</sup>I-MIBG; Cardiac Function; Heart Failure

## I. INTRODUCTION

In the normal heart, myocardial energy production largely depends on fatty acid (FA) metabolism under aerobic conditions [1]. However, FA oxidation is easily impaired by various pathological factors leading to heart failure (HF). Iodine-123-labeled 15-(p-iodophenyl)-3-(R, S)-methylpentadecanoic acid (<sup>123</sup>I-BMIPP) is a radioactive FA analog [2], and has been shown to be useful for evaluating the severity in patients with HF [3,4]. Myocardial uptake of <sup>123</sup>I-BMIPP was correlated with the grade of the New York Heart Association functional class [3]. Assessment of cardiac <sup>123</sup>I-BMIPP uptake was reported to be useful for predicting cardiac death in patients with chronic HF [5]. Thus, myocardial <sup>123</sup>I-BMIPP uptake provides not only the estimation of cardiac dysfunction but also prognostic information for cardiac events in patients with heart disease [4-6].

On the other hand, the activation of the central and peripheral sympathetic nervous systems is one of the major pathophysiological changes observed in patients with HF. Heart imaging with iodine-123 meta-iodobenzylguanidine (<sup>123</sup>I-MIBG), an analog of norepinephrine (NE), is used to evaluate abnormalities of cardiac sympathetic nerve activity in HF patients [7]. There is reduced myocardial accumulation and enhanced <sup>123</sup>I-MIBG washout in HF [8, 9]. The level of reduced cardiac uptake or enhanced washout of <sup>123</sup>I-MIBG is closely related to the HF severity [9]. Furthermore, it is reported that assessment by cardiac <sup>123</sup>I-MIBG uptake is useful for prognosis in HF patients [10].

The purpose of this study was to investigate how the degree of cardiac uptakes of <sup>123</sup>I-BMIPP or <sup>123</sup>I-MIBG was related to left ventricular (LV) functional parameters, particularly regarding diastolic function. The LV functional parameters were obtained by time–volume curve analysis from 16-frame gated myocardial single-photon emission computed tomography (SPECT) [11-13]. To assess cardiac prognosis, patients were followed up over 1500 days.

## II. METHODS

## A. Subjects

The studied patients were admitted to the Hospital of Shiga University of Medical Science due to worsening heart disease between 1 February 2004 and 31 June 2006 and underwent technetium-99m (Tc-99m) sestamibi and  $^{123}\text{I}$ -BMIPP or  $^{123}\text{I}$ -MIBG myocardial scintigraphic studies and could be followed up over 1500 days. The subjects with atrial fibrillation, atrial flutter and frequent premature contraction during SPECT data acquisition were excluded. In survival curve analysis, cardiac events were defined as death from worsening of heart failure or fatal arrhythmia due to heart disease. Thirty and 37 patients participated in the  $^{123}\text{I}$ -BMIPP and  $^{123}\text{I}$ -MIBG studies, respectively (Table 1). Because there were 12 patients who were included in both groups, we investigated a total of 55 patients (BMIPP + MIBG in Table 2). In a separate study, we examined 100 patients who underwent Tc-99m sestamibi myocardial perfusion scintigraphy for suspected heart diseases and had normal LV systolic function of EF  $\geq$ 50% (Normal EF in Table 2).

TABLE 1 PATIENT CHARACTERISTICS (1) BMI = BODY MASS INDEX, DCM = DILATED CARDIOMYOPATHY, HCM = HYPERTROPHIC CARDIOMYOPATHY, IHD = ISCHEMIC HEART DISEASE, OMI = OLD MYOCARDIAL INFARCTION

	BMIPP	MIBG
n	30	37
Age (years)	70.9 $\pm$ 7.6	64.3 $\pm$ 9.7
Male (n)	26	26
BMI (kg/m <sup>2</sup> )	23 $\pm$ 3	23 $\pm$ 4
Total cholesterol (mg/dl)	193 $\pm$ 37	186 $\pm$ 52
Triglyceride (mg/dl)	147 $\pm$ 75	156 $\pm$ 80
Creatinine (mg/dl)	0.98 $\pm$ 0.30	1.02 $\pm$ 0.48
HbA1c (%)	6.24 $\pm$ 1.20	5.95 $\pm$ 0.87
Heart rate (b.p.m.)	61.8 $\pm$ 5.4	62.1 $\pm$ 6.3
EF (%)	46.4 $\pm$ 20.3	40.3 $\pm$ 17.1
1/3FR (EDV/sec)	1.28 $\pm$ 0.61	1.13 $\pm$ 0.54
PFR (EDV/sec)	1.57 $\pm$ 0.72	1.35 $\pm$ 0.59
TPF (msec)	211 $\pm$ 100	206 $\pm$ 84
Disease		
IHD n(%)	12 (40)	3 (8)
OMI n(%)	8 (27)	3 (8)
Non IHD n(%)	18 (60)	34 (92)
DCM n(%)	8 (27)	20 (54)
HCM n(%)	4 (12)	5 (14)

TABLE 2 PATIENT CHARACTERISTICS (2) BMI = BODY MASS INDEX, DM = DIABETES MELLITUS, HTN = HYPERTENSION, IHD = ISCHEMIC HEART DISEASE

	BMIPP+ MIBG		Normal EF	
	Male	Female	Male	Female
n	41	14	60	40
Age (years)	66.0 $\pm$ 7.6	64.3 $\pm$ 13.0	66.6 $\pm$ 9.3	65.9 $\pm$ 10.1
BMI (kg/m <sup>2</sup> )	24 $\pm$ 4	21 $\pm$ 4	24 $\pm$ 3	24 $\pm$ 4
Total cholesterol (mg/dl)	181 $\pm$ 36	215 $\pm$ 67	180 $\pm$ 36	209 $\pm$ 48
Triglyceride (mg/dl)	165 $\pm$ 81	121 $\pm$ 65	139 $\pm$ 76	162 $\pm$ 70
Creatinine (mg/dl)	1.07 $\pm$ 0.35	0.82 $\pm$ 0.56	1.38 $\pm$ 1.73	0.94 $\pm$ 1.20
HbA1c (%)	6.07 $\pm$ 0.87	5.92 $\pm$ 1.16	6.33 $\pm$ 1.47	6.49 $\pm$ 1.62
Heart rate (b.p.m.)	61.0 $\pm$ 4.7	64.2 $\pm$ 9.2	61.5 $\pm$ 6.3	63.7 $\pm$ 9.2
EF (%)	40.0 $\pm$ 17.2	55.9 $\pm$ 18.7	65.9 $\pm$ 5.5	67.2 $\pm$ 7.1
Disease				
DM n(%)	27(45)	16(40)	19(46)	6(43)
IHD n(%)	37(62)	14(35)	11(27)	4(29)
HTN n(%)	43(72)	26(26)	20(49)	5(36)

B.  $^{123}\text{I}$ -BMIPP and  $^{123}\text{I}$ -MIBG Scintigraphy

$^{123}\text{I}$ -BMIPP (Nihon Medi-physics Co. Ltd., Hyogo, Japan) at a dose of 111 MBq was injected intravenously after at least 3-h fasting. Planar and single-photon emission computed tomography views were obtained 15 min after injection. A three-headed rotating gamma camera (GCA-9300A/UI; Toshiba Medical, Tokyo, Japan) equipped with a low-energy general

purpose collimator (system resolution, FWHM (full width at half maximum: 10.2 mm) and a medical image processor (GMS-5500 A/UI; Toshiba Co., Tokyo, Japan) was employed for image processing. The three-headed gamma camera rotated, collecting a total of 60 projections over 360°. Projection data were reconstructed into 64 × 64 matrix images by using the filter-back projection method with a Butterworth filter (order 8, cutoff 0.4 cycles/cm) and a ramp filter. The H/M count ratio was calculated from myocardial <sup>123</sup>I-BMIPP uptake ( $H_{BMIPP}$ ) and mediastinal <sup>123</sup>I-BMIPP uptake ( $M_{BMIPP}$ ) on anterior planar images by using the following equation:

$$H/M = H_{BMIPP}/M_{BMIPP}.$$

Similarly, <sup>123</sup>I-MIBG (FUJI FILM RI Pharma Co. Ltd., Tokyo, Japan) at a dose of 111 MBq was injected intravenously. Planar and single-photon emission computed tomography views were obtained 15 min (early) and 3 h (delayed) after tracer injection. The H/M count ratio was obtained from myocardial <sup>123</sup>I-MIBG uptake ( $H_{delay}$ ) and mediastinal <sup>123</sup>I-MIBG uptake ( $M_{delay}$ ) on anterior planar delayed images and was calculated using the following equation:

$$H/M = H_{delay}/M_{delay}.$$

<sup>123</sup>I-MIBG washout rate (WR) was calculated from myocardial <sup>123</sup>I-MIBG uptake on the early image ( $H_{early}$ ) and myocardial <sup>123</sup>I-MIBG uptake on the delayed image ( $H_{delay}$ ).

$$WR = [(H_{early} - H_{delay})/H_{early}] \times 100(\%).$$

### C. Gated SPECT

A dose of 600 MBq Tc-99m sestamibi (FUJI FILM RI Pharma Co. Ltd., Tokyo, Japan) was administered intravenously under resting conditions. One hour after tracer injection, quantitative electrocardiograph (ECG)-gated SPECT (QGS) images were acquired. A three-headed rotating gamma camera (GCA-9300A/UI) equipped with a low-energy high-resolution collimator (system resolution, FWHM: 7.7 mm) and a medical image processor (GMS-5500 A/UI) was employed for image processing. As the gamma camera rotated, it collected 60 projections over 360°. The projection data were reconstructed into 64 × 64 matrix images using the filter-back projection method with a Butterworth filter (order 8, cutoff 0.4 cycles/cm) and a ramp filter. A cardiac cycle was divided into 16 frames, and an average R-R interval of ±15% was allowed for gating. For data analysis the QGS program (Cedars-Sinai Medical Center, Los Angeles, CA, USA), which was previously described and validated by Germano et al. [13, 14], was applied to process short-axis tomograms to determine the LV end-diastolic volume (EDV), end-systolic volume, and EF. The LV volume data for each of the 16 frames calculated by the QGS program were manually entered into the VCDiff program (FUJIFILM RI Pharma Co. Ltd., Tokyo, Japan). The LV time–volume curves from 16-frame data were generated by Fourier curve-fitting analysis with the use of 5 harmonics. Cardiac parameters were automatically calculated from the time–volume curve and its differentiation curve (dV/dt) [11,12]. LV ejection fraction (EF) was assessed as a systolic functional parameter, and first third filling rate (1/3FR), peak filling rate (PFR), and time to peak filling (TPF) were estimated as diastolic functional parameters. The 1/3FR was assessed as the filling fraction during the first third of diastole. PFR was defined as the maximum dV/dt value divided by EDV/s, and TPF was measured from the time at end systole to the time at PFR (ms).

### D. Statistical Analysis

Data are expressed as means ± S.D. The correlations between parameters were examined using univariate and stepwise multivariate linear regression analyses. Single comparisons were performed with Student's unpaired t-test. Kaplan–Meier analysis was performed to determine cumulative survival rate from cardiac death. The patients were divided into 2 groups using 4 thresholds: a cardiac <sup>123</sup>I-BMIPP uptake of 2.4, which was the median value of H/M in this study; a cardiac <sup>123</sup>I-MIBG uptake of 2.2, which was derived from the intermediate H/M ratio of control and heart failure subjects in our previous study [15]; a PFR value of 1.7 EDV/s, which was reported to be the threshold of PFR by Akincioglu et al. [13]; and a TPF value of 170 ms, which was chosen because the Japanese Society of Nuclear Medicine database indicates normal TPF value of 176 ms in ≥60-year-old subjects [16] and Akincioglu et al. reported a normal TPF value of 165 ms [13]. Survival curves were compared using the log-rank test. A value of  $p < 0.05$  was considered statistically significant.

## III. RESULTS

### A. LV Function and Myocardial <sup>123</sup>I-BMIPP Uptake

Fig. 1 shows the relationships between myocardial <sup>123</sup>I-BMIPP uptake and LV functional parameters in 30 patients. Myocardial <sup>123</sup>I-BMIPP uptake (H/M) was positively correlated with EF ( $r = 0.57$ ,  $p = 0.0010$ ), 1/3FR ( $r = 0.46$ ,  $p = 0.0097$ ), and PFR ( $r = 0.47$ ;  $p = 0.0094$ ). There was no significant correlation between myocardial <sup>123</sup>I-BMIPP uptake and TPF.

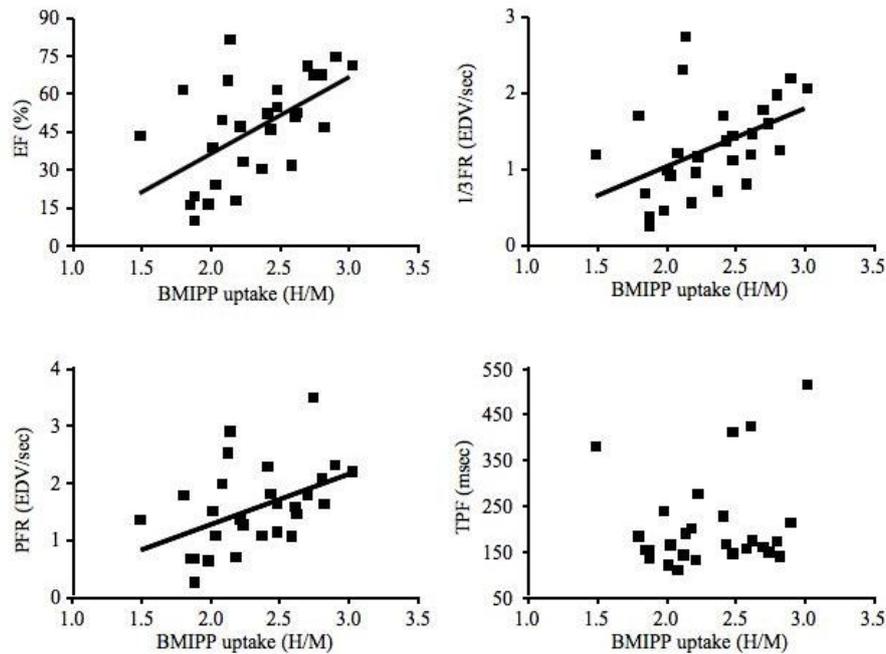


Fig. 1 Relationships between myocardial  $^{123}\text{I}$ -BMIPP uptake and left ventricular functional parameters (EF, 1/3FR, PFR, and TPF) in 30 patients. Myocardial  $^{123}\text{I}$ -BMIPP uptake (heart-to-mediastinum count ratio, H/M) was positively correlated with EF ( $r = 0.57$ ,  $p = 0.0010$ ), 1/3FR ( $r = 0.46$ ,  $p = 0.0097$ ), and PFR ( $r = 0.47$ ;  $p = 0.0094$ ). There was no significant correlation between myocardial  $^{123}\text{I}$ -BMIPP uptake and TPF.

### B. LV Function and Myocardial $^{123}\text{I}$ -MIBG Uptake

Fig. 2 shows the relationships between myocardial  $^{123}\text{I}$ -MIBG uptake and LV functional parameters in 37 patients. Myocardial  $^{123}\text{I}$ -MIBG uptake (H/M) was positively correlated with EF ( $r = 0.56$ ,  $p = 0.0003$ ), 1/3FR ( $r = 0.52$ ,  $p = 0.0012$ ), and PFR ( $r = 0.44$ ,  $p = 0.0058$ ). There was no significant correlation between myocardial  $^{123}\text{I}$ -MIBG uptake and TPF. Fig. 3 shows the relationships between myocardial  $^{123}\text{I}$ -MIBG washout rate (WR) and LV functional parameters in 37 patients. Myocardial  $^{123}\text{I}$ -MIBG WR was negatively correlated with EF ( $r = -0.52$ ,  $p = 0.0010$ ), 1/3FR ( $r = -0.51$ ,  $p = 0.0013$ ), and PFR ( $r = -0.47$ ,  $p = 0.0031$ ). There was no significant correlation between myocardial  $^{123}\text{I}$ -MIBG WR and TPF.

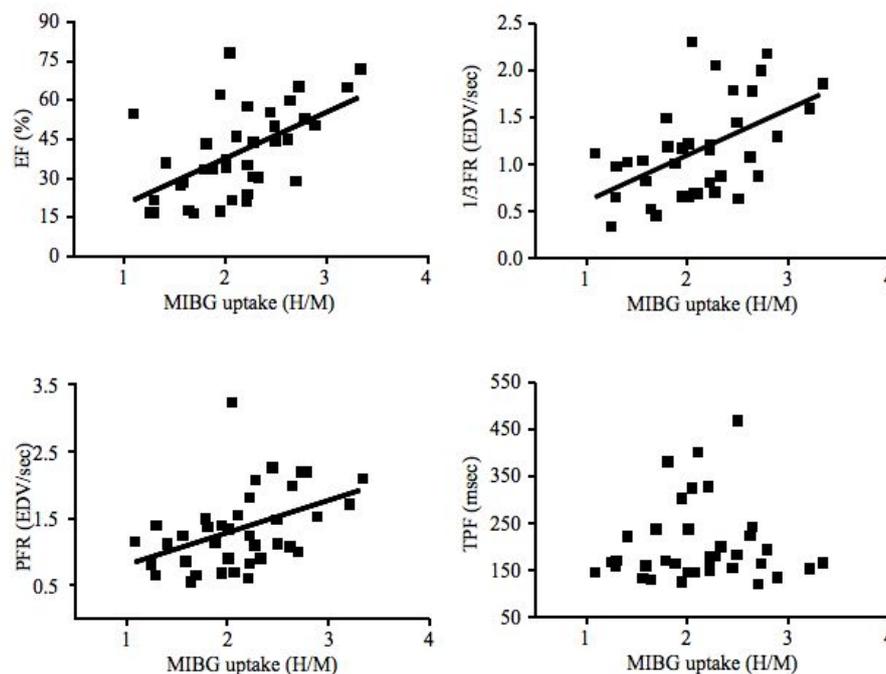


Fig. 2 Relationships between myocardial  $^{123}\text{I}$ -MIBG uptake and left ventricular functional parameters (EF, 1/3FR, PFR, and TPF) in 37 patients. Myocardial  $^{123}\text{I}$ -MIBG uptake (heart-to-mediastinum count ratio, H/M) was positively correlated with EF ( $r = 0.56$ ,  $p = 0.0003$ ), 1/3FR ( $r = 0.52$ ,  $p = 0.0012$ ), and PFR ( $r = 0.44$ ,  $p = 0.0058$ ). There was no significant correlation between myocardial  $^{123}\text{I}$ -MIBG uptake and TPF.

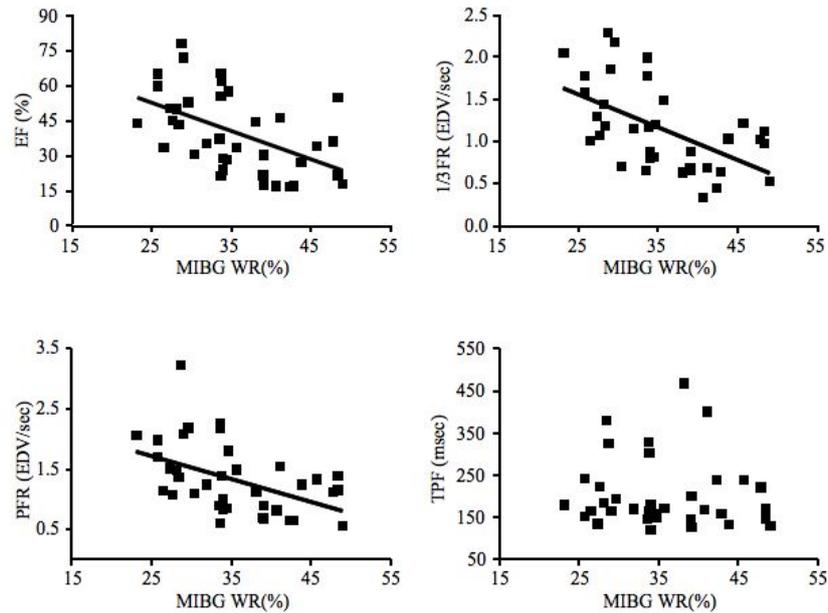


Fig. 3 Relationships between myocardial  $^{123}\text{I}$ -MIBG washout rate (WR) and left ventricular functional parameters (EF, 1/3FR, PFR, and TPF) in 37 patients. Myocardial  $^{123}\text{I}$ -MIBG washout rate (WR) was negatively correlated with EF ( $r = -0.52$ ,  $p = 0.0010$ ), 1/3FR ( $r = -0.51$ ,  $p = 0.0013$ ), and PFR ( $r = -0.47$ ,  $p = 0.0031$ ). There was no significant correlation between myocardial  $^{123}\text{I}$ -MIBG WR and TPF.

### C. LV Function and Age

Fig. 4 shows the relationships between age and LV functional parameters in the combined  $^{123}\text{I}$ -BMIPP and  $^{123}\text{I}$ -MIBG patients ( $n = 55$ ). There was no significant correlation between age and EF, 1/3FR, or PFR. However, age was positively correlated with TPF ( $r = 0.29$ ,  $p = 0.029$ ). In addition, there was a significant correlation between EF and both 1/3FR ( $r = 0.50$ ,  $p < 0.0001$ ) and PFR ( $r = 0.48$ ,  $p < 0.0001$ ) by univariate linear regression analysis; there was no significant correlation between EF and TPF (figure not shown). These findings were also examined in 100 separate patients (men,  $n = 60$ ; women,  $n = 40$ ) with normal systolic function ( $\text{EF} \geq 50\%$ ). Fig. 5 shows the relationships between age and LV functional parameters in these patients. Similar to the findings obtained in the combined  $^{123}\text{I}$ -BMIPP and  $^{123}\text{I}$ -MIBG patients, there was no significant correlation between age and EF, 1/3FR, or PFR. However, age was positively correlated with TPF ( $r = 0.26$ ,  $p = 0.0088$ ). In addition, there was a significant difference between EF and 1/3FR ( $r = 0.85$ ,  $p < 0.0001$ ) and PFR ( $r = 0.85$ ,  $p < 0.0001$ ) by univariate linear regression analyses, but not between EF and TPF (figure not shown).

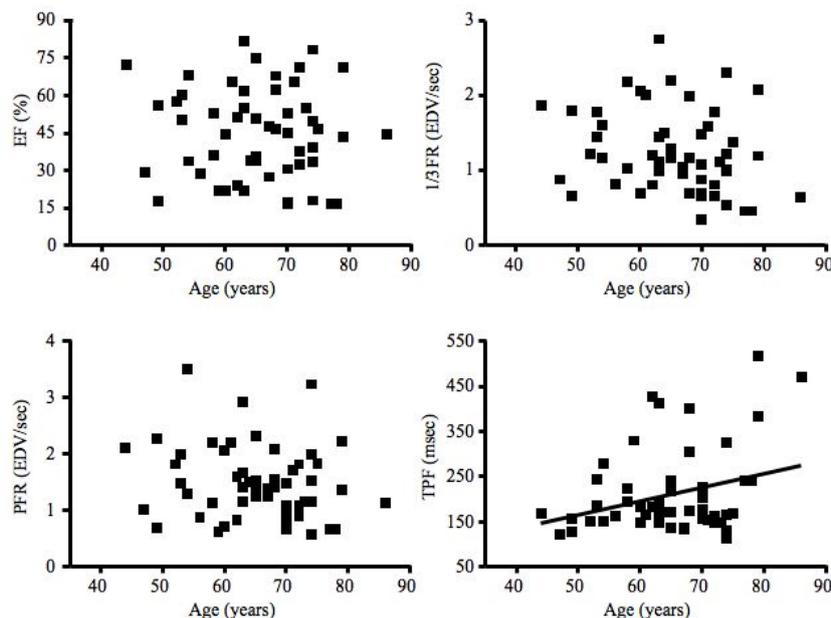


Fig. 4 Relationships between age and left ventricular functional parameters (EF, 1/3FR, PFR, and TPF) in the combined  $^{123}\text{I}$ -BMIPP and  $^{123}\text{I}$ -MIBG patients ( $n = 55$ ). There was no significant correlation between age and EF, 1/3FR, or PFR. However, age was positively correlated with TPF ( $r = 0.29$ ,  $p = 0.029$ ).

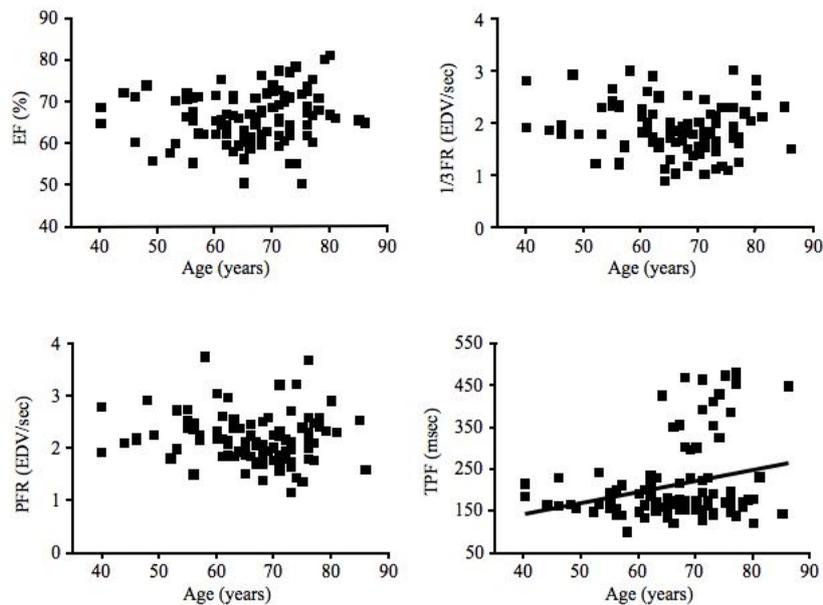


Fig. 5 Relationships between age and left ventricular functional parameters (EF, 1/3FR, PFR, and TPF) in 100 separate patients with normal systolic function (EF  $\geq$  50%). Similar to the findings in the combined  $^{123}\text{I}$ -BMIPP and  $^{123}\text{I}$ -MIBG patients, there was no significant correlation between age and EF, 1/3FR, or PFR. However, age was positively correlated with TPF ( $r = 0.26$ ,  $p = 0.0088$ ).

#### D. LV Function and Gender

Fig. 6 shows gender differences in EF, 1/3FR, PFR, and TPF in the combined  $^{123}\text{I}$ -BMIPP and  $^{123}\text{I}$ -MIBG patients ( $n = 55$ ) as well as in patients with normal EF ( $n = 100$ ). In the combined  $^{123}\text{I}$ -BMIPP and  $^{123}\text{I}$ -MIBG patients, EF, 1/3FR, and PFR were significantly higher in women than in men (women [ $n = 14$ ] vs. men [ $n = 41$ ]; EF,  $55.9 \pm 18.7\%$  vs.  $40.0 \pm 17.2\%$ ,  $p < 0.05$ ; 1/3FR,  $1.55 \pm 0.60$  vs.  $1.11 \pm 0.52$  EDV/s,  $p < 0.05$ ; PFR,  $1.83 \pm 0.68$  vs.  $1.35 \pm 0.62$  EDV/s,  $p < 0.05$ ). Although LV function was more preserved in women than in men as judged by these parameters, TPF was significantly longer in women than in men ( $256 \pm 127$  vs.  $196 \pm 76$  ms,  $p < 0.05$ ). Multivariable linear regression analysis showed that EF ( $\beta = 0.014$ ; SE = 0.004;  $p < 0.05$ ) was an independent predictor of PFR, but age and female gender were not; meanwhile, age ( $\beta = 3.30$ ; SE = 1.30;  $p < 0.05$ ) and female gender ( $\beta = -65.8$ ; SE = 26.9;  $p < 0.05$ ) were independent predictors of TPF, whereas EF was not. Furthermore, in patients with normal EF, there were no significant differences in EF, 1/3FR, or PFR between women and men (women [ $n = 40$ ] vs. men [ $n = 60$ ]; EF,  $67.2 \pm 7.1\%$  vs.  $65.9 \pm 5.5\%$ ; 1/3FR,  $1.88 \pm 0.44$  vs.  $1.91 \pm 0.49$  EDV/s; PFR,  $2.30 \pm 0.64$  vs.  $2.20 \pm 0.46$  EDV/s). However, TPF was significantly longer in women than in men ( $235 \pm 113$  vs.  $199 \pm 78$  ms,  $p < 0.05$ ). When multivariable linear regression analysis was applied to patients with normal EF, EF ( $\beta = 0.029$ ; SE = 0.007;  $p < 0.05$ ) was an independent predictor of PFR, whereas age and female gender were not; meanwhile, age ( $\beta = 2.31$ ; SE = 0.91;  $p < 0.05$ ) and female gender ( $\beta = -35.9$ ; SE = 17.4;  $p < 0.05$ ) were independent predictors of TPF, whereas EF was not.

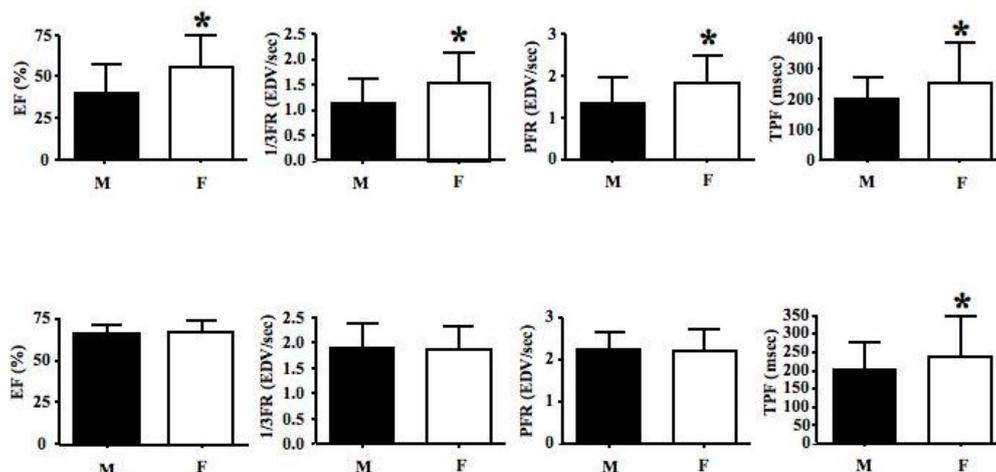


Fig. 6 Gender differences in EF, 1/3FR, PFR, and TPF in the combined  $^{123}\text{I}$ -BMIPP and  $^{123}\text{I}$ -MIBG patients (top,  $n = 55$ ), and in patients with normal EF (bottom,  $n = 100$ ). In the combined  $^{123}\text{I}$ -BMIPP and  $^{123}\text{I}$ -MIBG patients, EF, 1/3FR, and PFR were significantly higher in women ( $n = 14$ ) than in men ( $n = 41$ ). Nevertheless, TPF was significantly longer in women. In patients with normal EF, there were no significant differences in EF, 1/3FR, or PFR between women ( $n = 40$ ) and men ( $n = 60$ ). However, TPF was significantly longer in women. \* $p < 0.05$  vs. the values obtained in male gender.

### E. Survival Curve Analysis for the Cardiac Events

The patients were followed up over 1500 days; the mean  $\pm$  S.D. follow-up period was  $1177 \pm 486$  days. Of the 55 patients, 11 died from worsening of heart failure or fatal arrhythmia. In these 11 patients, the major clinical diagnoses were dilated cardiomyopathy (DCM,  $n = 6$ ), cardiac sarcoidosis ( $n = 1$ ), and old myocardial infarction (OMI,  $n = 4$ ). Fig. 7 shows the survival analysis for these patients. The group with  $^{123}\text{I}$ -BMIPP H/M ratios  $< 2.4$  ( $n = 15$ ) had a significantly ( $p = 0.029$ , log-rank test) lower survival rate than those with H/M ratios  $\geq 2.4$  ( $n = 15$ ). The group with  $^{123}\text{I}$ -MIBG H/M ratios  $< 2.2$  ( $n = 20$ ) had a significantly ( $p = 0.032$ ) lower survival rate than those with H/M ratios  $\geq 2.2$  ( $n = 17$ ). The group with PFR  $< 1.7$  EDV/s ( $n = 35$ ) had a significantly ( $p = 0.030$ ) lower survival rate than that with PFR  $\geq 1.7$  EDV/s ( $n = 20$ ). The group with TPF  $\geq 170$  ms ( $n = 28$ ) had a significantly ( $p = 0.029$ ) lower survival rate than that with TPF  $< 170$  ms ( $n = 27$ ).

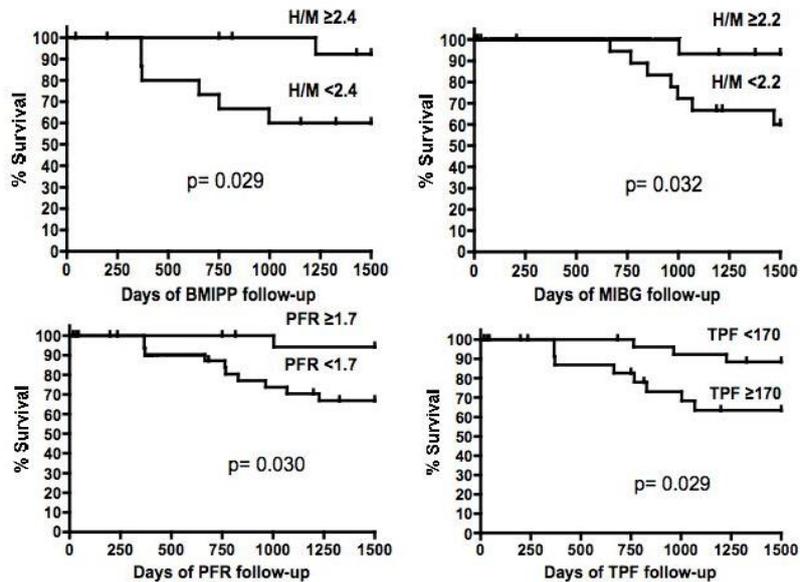


Fig. 7 Kaplan–Meier analysis for percent survival from various cardiac causes. Patients were divided into 2 groups according to  $^{123}\text{I}$ -BMIPP myocardial uptake (H/M, left, top),  $^{123}\text{I}$ -MIBG myocardial uptake (H/M, right, top), PFR (left, bottom), and TPF (right, bottom).

## IV. DISCUSSION

### A. Major Findings

In the present study, we examined the influence of myocardial  $^{123}\text{I}$ -BMIPP and  $^{123}\text{I}$ -MIBG uptake on LV function—specifically the systolic functional parameter, EF, and the diastolic functional parameters, 1/3FR, PFR, and TPF.  $^{123}\text{I}$ -BMIPP and  $^{123}\text{I}$ -MIBG uptake, and  $^{123}\text{I}$ -MIBG WR were all correlated with EF, 1/3FR, and PFR but not TPF. TPF was positively correlated with age, but EF, 1/3FR, or PFR was not in the combined  $^{123}\text{I}$ -BMIPP and  $^{123}\text{I}$ -MIBG patients (mean EF,  $43.8 \pm 18.9\%$ ) and also in patients with normal EF. TPF was longer in women than in men, regardless of EF. Despite these difference, Kaplan–Meier analysis identified earlier cardiac events in the case of patients with lower H/M ratios for  $^{123}\text{I}$ -BMIPP and  $^{123}\text{I}$ -MIBG, lower PFR, and prolonged TPF values.

### B. Methodological Limitations

In the present study, LV systolic and diastolic functions were assessed using gated myocardial SPECT with 16 framing data acquisition. Previous studies indicated that functional parameters from the QGS data with 16 frames tended to be underestimated when compared to those from the QGS data with 32 frames [17]. However, recent studies have suggested that impact of fewer frames on functional parameters is less than that previously thought of [13,16]. Akincioglu et al. calculated normal values of LV diastolic functional parameters using 16-frame gated myocardial perfusion SPECT, and showed that these values were similar to those reported with gated blood-pool studies [13]. We previously compared LV diastolic functional parameters obtained from the 16-frame gated SPECT data with those obtained by echocardiography, and reported a significant correlation between diastolic parameters measured by these 2 methods [11]. Thus, we believe that diastolic parameters from 16-frame QGS data are acceptable at least in clinical use.

### C. Myocardial $^{123}\text{I}$ -BMIPP Uptake and LV Function

In the present study, myocardial  $^{123}\text{I}$ -BMIPP uptake was positively correlated with EF, 1/3FR, and PFR but not TPF. We

previously examined the relationship between myocardial  $^{123}\text{I}$ -BMIPP uptake and LVEF estimated by using echocardiography in HF patients [4]. As for the LV systolic functional parameter EF, the finding was similar to that in our previous study, i.e., a positive correlation between cardiac  $^{123}\text{I}$ -BMIPP uptake and LVEF [4]. However,  $^{123}\text{I}$ -BMIPP uptake affected the LV diastolic functional parameters 1/3FR, PFR, and TPF differently in the present study. It appears that TPF exhibits a unique behavior independent of the other diastolic parameters. This may be attributable to the fact that cardiac dilatation involves a complex interaction of both active and passive processes [18, 19]. The diastolic characteristics of the heart are composed of 2 aspects: relaxation and wall stiffness. Early diastole is basically an active energy-dependent (i.e., ATP-requiring) process, and its functional class may be well reflected by 1/3FR. In contrast, ventricular stiffness or compliance is generally measured at end diastole, and its functional class may be well reflected by TPF. PFR is probably affected by both components. Thus, it appears that altered FA metabolism basically influences an active, energy-dependent process in cardiac performance, which is reasonable because FA is the principal energy source of the heart.

#### D. Myocardial $^{123}\text{I}$ -MIBG Uptake and LV Function

In the present study, cardiac  $^{123}\text{I}$ -MIBG uptake correlated positively with EF, 1/3FR and PFR, but not with TPF; similarly to the results of the  $^{123}\text{I}$ -BMIPP study, and  $^{123}\text{I}$ -MIBG WR correlated negatively with EF, 1/3FR and PFR, but not with TPF. An elevation of circulating NE may compete with  $^{123}\text{I}$ -MIBG uptake at the receptor site in HF, resulting in decreased cardiac  $^{123}\text{I}$ -MIBG uptake. It has been reported that in HF, myocardial accumulation of  $^{123}\text{I}$ -MIBG is reduced and its washout is enhanced. Merlet et al. reported that cardiac  $^{123}\text{I}$ -MIBG uptake (delayed H/M) correlates with LVEF in patients with HF [10]. Imamura et al. reported that the WR of  $^{123}\text{I}$ -MIBG correlates with PFR and cardiac index [9, 20]. Delayed H/M ratio is affected by both the initial uptake and washout of  $^{123}\text{I}$ -MIBG. Our results regarding EF and PFR were compatible with the above studies. Thus, an impairment of sympathetic nerve activity may also be related to an active, energy-dependent process in cardiac performance in patients with heart disease. TPF did not correlate with the H/M and WR of  $^{123}\text{I}$ -MIBG. Instead, prolonged TPF was related to aging and gender differences as described below.

#### E. LV Function and Age

In the present study, age was positively correlated with TPF but not with EF, 1/3FR, or PFR in the combined  $^{123}\text{I}$ -BMIPP and  $^{123}\text{I}$ -MIBG patients with a mean EF of 43.8%. Because this group included many patients with decreased EF (EF < 45%, n = 28), the decreased systolic function itself might directly affect diastolic function. Therefore, the relationship between age and TPF was also examined in patients with normal EF and produced similar findings.

With physiological aging, the LV undergoes tonic structural and functional changes that include increases in wall thickness and chamber diameter, concentric remodeling, and increased mass; these result in reduced diastolic function [21]. Alterations in TPF were unrelated to alterations in EF. Thus, prolonged TPF probably reflects the increase in the LV wall stiffness related to aging. In our previous study, TPF and not EF was related to the degree of arterial stiffness, which suggests age-related physiological changes [12].

Akincioglu et al. assessed diastolic function using 16-frame  $^{99\text{m}}\text{Tc}$ -sestamibi gated myocardial perfusion SPECT and reported that age, gender, and LVEF are independent predictors of PFR in normal subjects, whereas TPF is not influenced by any clinical or systolic functional variables [13]. In that study, subjects were excluded if they had hypertension (HTN), diabetes mellitus (DM), ECG abnormality, or known cardiac disease. In our study, LVEF was correlated with PFR but not TPF, which is consistent with the findings reported by Akincioglu et al. However, our study showed that TPF was correlated with age and was higher in women than in men, and this finding is inconsistent with that reported by Akincioglu et al. [13]. Although the reason behind this discrepancy is unclear, it is worth noting that unlike the present study, the study by Akincioglu et al. excluded HTN, DM, ECG abnormality, and known cardiac disease. This difference may account for the discrepancy between the results of the 2 studies. At present, the prevalence of HTN and DM increases with age. Many people older than 60 years may have such complications. Our results suggest that if complications such as HTN, DM, or heart disease are present, prolonged TPF may increase with age.

#### F. LV Function and Gender

In the present study, TPF was significantly longer in women than in men, regardless of the EF value. An epidemiological study showed that the incidence of HF increases dramatically in women older than 55 and that diastolic HF (or HF with preserved EF) is more predominant in women. The prolonged TPF caused by aging and related to female gender regardless of EF value may thus be related to the occurrence of diastolic HF in elderly women. Although age, HTN, DM, OMI, and myocardial hypertrophy are well-known major risk factors of HF, it has been shown that the contribution of each of these risk factors differs between women and men [22-24]. Women often exhibit HTN and DM [22]; HTN causes HF more frequently in women than in men [23]. Obesity, DM, and impaired glucose tolerance also increase the risk of HF in women, and these risk factors may impair myocardial metabolism more profoundly in women than in men [24]. Because our patients had HTN, DM, or ischemic heart disease (IHD), prolonged TPF may be more prevalent in women than in men. In support of this idea, Okura et al. investigated the gender specificity of age-related LV diastolic dysfunction by using echocardiography and reported that

diastolic function deteriorates more profoundly in women than in men in the elderly population [25]. This might partially account for the prolonged TPF observed in our study. However, because the number of studied subjects was small, further examinations are needed.

### G. Kaplan–Meier Survival Analysis

In the present study, cardiac events occurred earlier in patients with a lower H/M of  $^{123}\text{I}$ -BMIPP. Sasaki et al. showed that the H/M of  $^{123}\text{I}$ -BMIPP can predict cardiac death in HF patients in a 660-day follow-up period [5]. Previously, we also reported earlier HF progression for patients with lower H/M of  $^{123}\text{I}$ -BMIPP [4]. Inoue et al. reported that the extent score of  $^{123}\text{I}$ -BMIPP is a useful predictor of cardiac events in DCM [4]. Thus, our findings are corroborated by previous reports.

Furthermore, in the present study, earlier occurrence of cardiac events was observed in patients with a lower H/M of  $^{123}\text{I}$ -MIBG. Merlet et al. reported that lower  $^{123}\text{I}$ -MIBG H/M values was an important index for predicting poor prognoses in HF patients with ischemic or idiopathic cardiomyopathy [10]. Tamaki et al. showed that cardiac MIBG imaging predicts sudden cardiac death independently of LVEF in patients with chronic HF [26]. Thus, our findings are corroborated by previous reports.

The present study also showed the earlier occurrence of cardiac events in the case of patients with lower PFR values. LVEF has been shown to be a potent prognostic marker in HF patients such as those with DCM [10, 27]. Such a finding is reasonable considering that PFR is significantly correlated with EF.

In the present study, an earlier occurrence of cardiac events was found for patients with prolonged TPF. PFR depends on LVEF, whereas TPF does not. Nevertheless, both TPF and PFR may provide useful prognostic information. As described above, prolonged TPF may be related to the occurrence of diastolic HF in elderly women. LV diastolic dysfunction basically involves slowed LV relaxation, increased LV stiffness, or abnormal LV filling. Adequate LV filling is essential for maintaining normal cardiac output. Therefore, if tachycardia (e.g., paroxysmal atrial fibrillation) occurs, a prolonged TPF may reduce the ability of the heart to achieve adequate output even if systolic function is preserved. The present study found that when patients with HTN, DM, or IHD were included, TPF increased with age and was longer in women. These characteristics are in agreement with the epidemiologic profile of diastolic HF. Our results suggest that even though the diastolic parameters TPF and PFR behave differently, they both provide prognostic information for cardiac events. However, because the number of studied subjects was small, further examinations are needed.

## V. CONCLUSION

The degree of decreased cardiac uptakes of FA and NE may be associated with the grade of systolic and diastolic dysfunctions assessed by EF, PFR, and 1/3FR. In contrast, prolonged TPF is caused by aging and female gender, regardless of EF value; consequently, prolonged TPF may be related to the occurrence of diastolic HF in elderly women. Thus, our study suggests that  $^{123}\text{I}$ -BMIPP and  $^{123}\text{I}$ -MIBG uptake, age, and gender influence LV function in different ways. Despite their differences, decreased  $^{123}\text{I}$ -BMIPP and  $^{123}\text{I}$ -MIBG uptake, decreased PFR, and prolonged TPF may all indicate poor cardiac prognosis in patients with heart disease.

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