



# Prognostic value of left ventricular mechanical dyssynchrony induced by exercise stress in patients with normal myocardial perfusion single-photon emission computed tomography

Tomohiko Sakatani, MD, PhD,<sup>a</sup> Takeru Kasahara, MD,<sup>a</sup>  
Daisuke Irie, MD, PhD,<sup>a</sup> Yoshinori Tsubakimoto, MD, PhD,<sup>a</sup>  
Akiko Matsuo, MD,<sup>a</sup> Hiroshi Fujita, MD, PhD,<sup>b</sup> and Keiji Inoue, MD, PhD<sup>a</sup>

<sup>a</sup> Department of Cardiology, Japanese Red Cross Kyoto Daini Hospital, Kyoto, Japan

<sup>b</sup> Department of Cardiology, North Medical Center, Kyoto Prefectural University of Medicine, Kyoto, Japan

Received Jul 5, 2020; accepted Sep 17, 2020  
doi:10.1007/s12350-020-02389-6

**Background.** Left ventricular mechanical dyssynchrony (LVMD) induced by exercise stress was reported to be clinically useful in detecting multivessel coronary artery diseases. The aim of this study was to compare the prognostic value of LVMD induced by pharmacological stress with that induced by exercise stress.

**Methods.** We retrospectively examined 918 consecutive patients who underwent exercise (N = 310) or pharmacological stress (N = 608) <sup>99m</sup>Tc-tetrofosmin single-photon emission computed tomography (SPECT) with normal myocardial perfusion. LVMD was evaluated by phase analysis as the indices of phase bandwidth and phase standard deviation (PSD).

**Results.** During the follow-up period (2.2 ± 1.9 years), 74 major cardiac events (MCEs) occurred (7 cases of cardiac death, 17 cases of heart failure, and 50 cases of coronary intervention). In global patients, the indices of LVMD on rest images were significantly greater in patients with MCEs (bandwidth (°): 51 ± 31 vs 37 ± 21, P = .001, PSD: 14 ± 9 vs 10 ± 6, P = .001). The exercise stress bandwidth was significantly higher in patients with MCEs (62 ± 37° vs 42 ± 21°, P = .026), as was the pharmacological stress bandwidth (57 ± 35° vs 43 ± 24°, P = .006). Multivariate analysis demonstrated the exercise stress bandwidth to be an independent predictor of MCEs (HR 1.017, CI 1.003 to 1.032, P = .019), but the pharmacological stress bandwidth had no influence on MCEs.

**Conclusions.** LVMD induced by exercise stress was an independent predictor of MCEs in patients with normal perfusion SPECT, whereas that induced by pharmacological stress had no association with further events. (J Nucl Cardiol 2022;29:965–74.)

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s12350-020-02389-6>) contains supplementary material, which is available to authorized users.

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All editorial decisions for this article, including selection of reviewers and the final decision, were made by guest editor Saurabh Malhotra, MD, MPH.

**Funding** Not applicable.

Reprint requests: Tomohiko Sakatani, MD, PhD, Department of Cardiology, Japanese Red Cross Kyoto Daini Hospital, 355-5 Haruobi-cho, Kamigyo-Ku, Kyoto 602-8026, Japan; [sakatani@koto.kpu-m.ac.jp](mailto:sakatani@koto.kpu-m.ac.jp)

1071-3581/\$34.00

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**Key Words:** <sup>99m</sup>Tc-tetrofosmin • phase analysis • exercise and pharmacological stress • cardiac events

Abbreviations	
LVMD	Left ventricular mechanical dyssynchrony
SPECT	Single-photon emission computed tomography
PSD	Phase standard deviation
MCEs	Major cardiac events
TDI	Tissue Doppler imaging
MPS	Myocardial perfusion SPECT
CAD	Coronary artery diseases
QGS	Quantitative-gated SPECT
LVEF	Left ventricular ejection fraction

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## INTRODUCTION

Left ventricular mechanical dyssynchrony (LVMD) is a conduction disturbance characterized by a wide QRS duration on electrocardiography. The degree of LVMD was analyzed by tissue Doppler imaging (TDI) assessed by echocardiography. Myocardial perfusion single-photon emission computed tomography (SPECT) (MPS) is able to analyze LVMD quantitatively by phase analysis.<sup>1</sup> The indices of LVMD, such as phase standard deviation (PSD) and phase bandwidth, are well correlated with those measured by tissue Doppler imaging.<sup>2-4</sup> The prognostic value for major cardiac events (MCEs) of LVMD was previously demonstrated in asymptomatic women,<sup>5</sup> patients with systolic heart failure,<sup>6</sup> and in those with acute coronary syndrome.<sup>7</sup>

Normal stress MPS findings are associated with low-cardiac event risk.<sup>8</sup> Myocardial perfusion sometimes globally reduces in patients with multivessel coronary artery diseases (CAD). Thus, there are some underestimated cases when MPS has no signs of cardiac ischemia. In those cases LVMD induced by exercise stress has diagnostic value in the detection of multivessel CAD.<sup>9</sup> However, it is unknown whether LVMD induced by pharmacological stress (hyperemic drugs) is associated with future events. In this study, we retrospectively investigated whether LVMD induced by exercise or pharmacological stress has prognostic value in patients with normal myocardial perfusion.

## METHODS

### Study Population

We retrospectively examined 918 consecutive patients who underwent exercise (N = 310) or

pharmacological stress (N = 608) <sup>99m</sup>Tc-tetrofosmin SPECT. All patients were scheduled to undergo stress-rest ECG-gated MPS due to possible or definite CAD. Patients with bundle branch block on electrocardiography and abnormal MPS (summed stress score  $\geq 3$ ) were excluded from this study. The endpoint was the incidence of MCEs consisting of cardiac death, non-fatal myocardial infarction, hospitalization due to heart failure, and coronary intervention due to acute coronary syndrome or worsening symptom of angina. The presence of cardiac events was followed up in all patients after MPS. The study was conducted in accordance with the standards of the local ethics committee. For this retrospective study design, formal consent was not required.

### Myocardial Perfusion SPECT Study

Pharmacological (adenosine) or exercise stress <sup>99m</sup>Tc-tetrofosmin SPECT was performed for each patient using a 1-day protocol. The dose of <sup>99m</sup>Tc-tetrofosmin was 296 MBq at stress imaging and 596 MBq at rest imaging. Stress was induced by ergometer and was stopped when the patient's heart rate reached more than 85% of the maximum predictive heart rate. Horizontal or downsloping ST-segment depression ( $\geq .1$  mV) on electrocardiogram was considered as positive exercise test. Pharmacological stress by adenosine with low-dose exercise (25 W) was used for patients with a low exercise tolerance. Patients were instructed not to consume caffeine for 24 hours before pharmacological stress. <sup>99m</sup>Tc-tetrofosmin was injected 1 minute before the end of exercise or 3 minutes after the start of adenosine (120  $\mu$ g/min and total 6 minutes). Stress and rest images were acquired 30 minutes after <sup>99m</sup>Tc-tetrofosmin injection. Four hours later, the rest image was acquired after re-injection of <sup>99m</sup>Tc-tetrofosmin.

### SPECT Acquisition Protocol

Stress and rest images were acquired on a dual-detector gamma camera (Siemens Medical Solutions, Erlangen, Germany) using a low-energy, high-resolution collimator. The gamma camera rotated, collecting 64 projections over 180° for 40 seconds per projection. The projection data were reconstructed into 64  $\times$  64 matrix images using the filtered back projection method. The quantitative-gated SPECT (QGS) software (Cedars Sinai Medical Center, CA, USA) was used for analysis of the left ventricular functional parameters [left ventricular

ejection fraction (LVEF) and end diastolic (EDV)/systolic volume (ESV)].

### Quantitative Data Analysis of Perfusion SPECT

The SPECT images were divided into 17 segments and scored visually using a 5-point scale. The summed stress and rest scores (SSS and SRS) were calculated by adding the scores of these segments of the left ventricle. The summed difference score (SDS) was calculated by SSS minus SRS. Normal myocardial perfusion SPECT was defined as an SSS of less than 3. To evaluate the degree of LVMD, we calculated two indices, the phase standard deviation (PSD) and bandwidth, by phase analysis using Heart Function View software (Nihon Medi-Physics. Co. Ltd., Tokyo, Japan). A phase distribution of the mechanical contraction onset at each regional left ventricular wall was generated, and the histogram bandwidth and PSD were calculated.<sup>9</sup>

### Statistical Analysis

Variables are expressed as the mean ± standard deviation. Normally distributed parameters were compared by t tests and non-normally distributed data were analyzed by the Mann–Whitney *U* test. Categorical data were compared using the Chi-square test. Multivariate analysis was performed by Cox proportional regression analysis, into which age, gender, LVEF, SSS, bandwidth at stress and combination with other cardiac diseases were entered. Event-free curves were calculated with Kaplan–Meier estimates and differences between two curves were evaluated using a log-rank test. A *P* value < .05 was considered significant.

## RESULTS

### Clinical Characteristics of the Patients

The characteristics of the study population are shown in Table 1. The mean age was 70 ± 12 years and the mean LVEF was 71 ± 11%. SSS, SRS, and SDS were .3 ± .7, .2 ± .6, and .2 ± .6, respectively. The QRS duration on electrocardiography was 98.0 ± 9.5 ms. Based on these results, all patients had neither evidence of cardiac ischemia on MPS nor notable LVMD on electrocardiography.

### Comparison Between Exercise and Pharmacological Stress

The characteristics of patients with exercise and pharmacological stress are shown in Table 2. Those

**Table 1.** Patient characteristics of the study population

Age (years)	70 ± 12
Gender (male:female)	496:422
BMI (kg/m <sup>2</sup> )	23.1 ± 3.6
eGFR (mL/min/1.73 m <sup>2</sup> )	63 ± 19
QRS duration (ms)	98.0 ± 9.5
Coronary risk, <i>n</i> (%)	
Hypertension	588 (64)
Dyslipidemia	488 (53)
Diabetes	240 (26)
Smoking	309 (34)
SPECT	
SSS	.3 ± .7
SRS	.2 ± .6
SDS	.2 ± .6
QGS	
EDV (mL)	79 ± 25
ESV (mL)	25 ± 16
LVEF (%)	71 ± 11

*BMI*, body mass index; *EDV*, end diastolic volume; *eGFR*, estimated glomerular filtration rate; *ESV*, end systolic volume; *LVEF*, left ventricular ejection fraction; *SDS*, summed differential score; *SRS*, summed rest score; *SSS*, summed stress score; *QGS*, quantitative-gated SPECT

with pharmacological stress were older (*P* < .001), had a lower eGFR (*P* = .004), and a higher EDV (*P* < .001) and ESV (*P* = .015). The proportion of male patients was larger in the exercise stress group (*P* = .001). In both groups, the patients had a normal LVEF by QGS and no evidence of LVMD by phase analysis.

### Cardiac Events During Follow-up

During the follow-up period of 2.2 ± 1.9 years, 74 MCEs occurred. Seven patients had cardiac death, 17 patients were hospitalized due to worsening heart failure, and 50 patients required coronary intervention due to acute coronary syndrome or worsening symptom of angina. The Kaplan–Meier event-free curve revealed that there was no significant difference in cardiac events between pharmacological and exercise stress (*P* = .108) (Figure 1). The comparison of the data with and without MCEs is shown in Table 3 ((A) global patients (N = 918), (B) pharmacological stress (N = 608), (C) exercise stress (N = 310)). The patients with MCEs were older (*P* < .001), and had lower LVEF (< .001) and greater SSS (*P* < .001) although all patients had no evidence of cardiac ischemia (SSS < 3) nor decreased cardiac function (Table 3A). The indices of LVMD on rest images were significantly greater in patients with MCEs

**Table 2.** Comparison between exercise and pharmacological stress

	Pharmacological stress (N = 608)	Exercise stress (N = 310)	P value
Age (years)	73 ± 11	64 ± 13	< .001
Gender, male (%)	305 (50.2)	191 (61.6)	.001
BMI (kg/m <sup>2</sup> )	23.0 ± 3.6	23.5 ± 3.4	.070
eGFR (mL/min)	62 ± 20	66 ± 15	.004
SPECT			
SSS	.3 ± .7	.3 ± .7	.423
SRS	.1 ± .6	.2 ± .6	.332
SDS	.2 ± .6	.1 ± .5	.034
QGS (mL)			
EDV (mL)	76 ± 26	84 ± 23	< .001
ESV (mL)	24 ± 17	27 ± 14	.015
LVEF (%)	71 ± 11	70 ± 9	.067
Stress			
Bandwidth (°)	44 ± 25	43 ± 23	.505
Phase SD	12 ± 7	12 ± 7	.461
Rest			
Bandwidth (°)	39 ± 24	38 ± 20	.445
Phase SD	11 ± 7	10 ± 6	.223
Coronary risk, n (%)			
Hypertension	425 (70)	164 (53)	< .001
Dyslipidemia	328 (54)	159 (51)	.164
Smoking	180 (30)	129 (42)	< .001
Diabetes	159 (26)	81 (26)	.994

BMI body mass index; EDV, end diastolic volume; eGFR, estimated glomerular filtration rate; ESV, end systolic volume; LVEF, left ventricular ejection fraction; SDS, summed differential score; SRS, summed rest score; SSS, summed stress score; QGS, quantitative-gated SPECT

(bandwidth (°): 51 ± 31 vs 37 ± 21, *P* = .001, PSD: 14 ± 9 vs 10 ± 6, *P* = .001). Similarly, the indices of LVMD on stress images were significantly greater in patients who experienced cardiac events in both pharmacological (bandwidth (°): 57 ± 35 vs 43 ± 24, *P* = .006; PSD: 16 ± 10 vs 12 ± 7, *P* = .011) and exercise (bandwidth (°): 62 ± 37 vs 42 ± 21, *P* = .026; PSD: 17 ± 12 vs 12 ± 6, *P* = .040) stress groups (Table 3B, C).

### Univariate and Multivariate Analyses

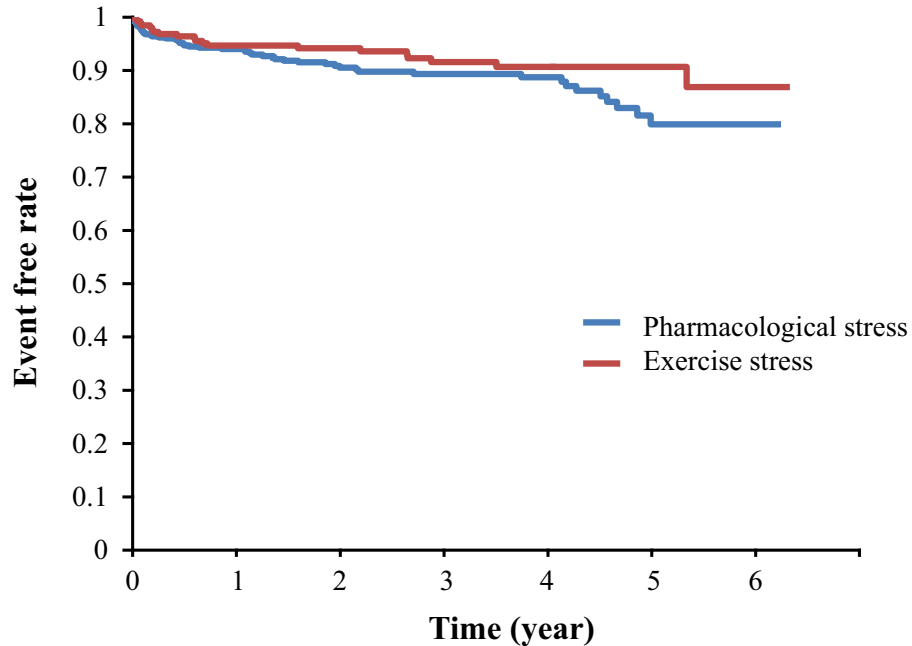
In global patients, the bandwidth at rest (*P* = .013), age (*P* < .001), gender (*P* = .043), LVEF (*P* = .003), and SSS (*P* = .004) were independent predictors of cardiac events (Table 4A). In patients with pharmacological stress, the bandwidth at stress (*P* = .004), age (*P* = .002), LVEF (*P* < .001), and SSS (*P* = .008) were univariate predictors of cardiac events (Table 4B). However, based on multivariate analysis, age (*P* = .002) and LVEF (*P* < .001), but not bandwidth, were independent predictors of

cardiac events. In patients with exercise stress, the bandwidth at stress (*P* = .002), LVEF (*P* = .013), and SSS (*P* < .001) were univariate predictors of cardiac events (Table 4C). Bandwidth at stress was also an independent predictor of cardiac events in multivariate analysis (*P* = .019).

### DISCUSSION

This is the first study to describe the prognostic value of bandwidth on exercise stress as an index of LVMD in patients with no evidence of cardiac ischemia. LVMD induced by exercise stress was associated with further cardiac events, whereas that induced by pharmacological stress was not.

LVMD is evaluated by the QRS duration on electrocardiography or by TDI assessed by echocardiography. Phase analysis on MPS is also one of the methods for evaluating LVMD. Heart Function View evaluates the phase distribution and regional left



No at risk

Pharmacological	608	367	261	186	116	47	12
Exercise	310	206	172	131	83	39	1

**Figure 1.** Kaplan–Meier event-free curve for the endpoint.

ventricular onset of mechanical contraction.<sup>10</sup> LVMD is quantitatively assessed by the indices such as PSD and bandwidth. The reference values in normal subjects of this software to evaluate the degree of LVMD were described in the previous report.<sup>11</sup> Normal upper limits of bandwidth and phase SD at rest images were 38° and 10°, respectively. In our study, mean values of bandwidth and phase SD in patients without cardiac events at rest images were 37° and 10°, respectively (Table 3A). Thus, normal cut-off values of bandwidth and phase SD based on the previous report might be applicable. LVMD assessed by MPS was previously reported to be well correlated with that assessed by TDI.<sup>2</sup> The assessment of LVMD is important to select patients for cardiac resynchronization therapy (CRT). TDI was prevalent as the evaluation method of LVMD because of its non-invasive nature, but CRT guided by TDI had negative results due to lack of reproducibility.<sup>12,13</sup> Phase analysis on MPS just after CRT can predict the CRT response.<sup>14</sup>

Normal stress MPS findings in the Japanese population are associated with low-cardiac event risk.<sup>8</sup> However, 74 patients (8.1%), including 50 with coronary intervention, had cardiac events in our study. No focal perfusion defect was observed because of a global reduction in patients with left main or 3-vessel CAD.

LVMD induced by exercise stress was reported in patients with multivessel CAD.<sup>9</sup> LV ischemic myocardium induced by exercise stress contracts weaker than the other non-ischemic wall. The strong wall pushes out the weaker wall, which leads to delayed contraction of the weak wall. Accordingly, LVMD may develop in association with cardiac ischemia induced by exercise stress even with a pseudo-normal MPS and multivessel CAD. On the other hand, adenosine increases the volume of microvascular circulation and it is not considered to induce actual myocardial ischemia despite the development of reversible perfusion defects. No significant stress-induced alteration within the indices of mechanical dyssynchrony using phase analysis was observed in the majority of patients (70%) evaluated under pharmacological stress.<sup>15</sup> However, there are conflicting results about LVMD induced by pharmacological stress. A previous report demonstrated that the maximum difference in time to end-systole, which was defined as the index of LVMD in that study, in the 17 segments increased after adenosine loading in CAD patients, but not in normal subjects.<sup>16</sup> That study suggested that adenosine has the ability to induce LVMD, but LVMD was evaluated by the time volume curve, not by phase analysis. Dobutamine has also been used for pharmacological stress. In patients with heart

**Table 3.** Comparison between patients with and without cardiac events in global patients (A), pharmacological (B) and exercise (C) stress groups

<b>(A)</b>	<b>With cardiac event (N = 74)</b>	<b>Without cardiac event (N = 844)</b>	<b>P value</b>
Age (years)	75 ± 9	69 ± 12	< .001
Gender, male (%)	58 (78.4)	438 (51.9)	< .001
BMI (kg/m <sup>2</sup> )	22 ± 4	23 ± 4	.32
QGS			
EDV (mL)	92 ± 40	78 ± 23	.003
ESV (mL)	38 ± 32	24 ± 14	< .001
LVEF (%)	64 ± 15	72 ± 21	< .001
SPECT			
SSS	.7 ± .9	.3 ± .7	< .001
SRS	.3 ± .6	.1 ± .6	.142
SDS	.4 ± .8	.2 ± .7	.003
Rest			
Bandwidth (°)	51 ± 31	37 ± 21	.001
Phase SD	14 ± 9	10 ± 6	.001
Coronary risk, n (%)			
Hypertension	47 (87)	378 (68)	.004
Dyslipidemia	34 (63)	294 (53)	.164
Smoking	25 (46)	155 (28)	.005
Diabetes	19 (35)	140 (25)	.114
<b>(B)</b>	<b>With cardiac event (N = 54)</b>	<b>Without cardiac event (N = 554)</b>	<b>P value</b>
Age (years)	77 ± 7	72 ± 11	< .001
Gender, male (%)	38 (70.3)	267 (48.2)	.002
BMI (kg/m <sup>2</sup> )	22 ± 4	23 ± 4	.320
QGS			
EDV (mL)	90 ± 44	75 ± 23	.014
ESV (mL)	38 ± 35	23 ± 14	.002
LVEF (%)	64 ± 16	72 ± 25	.001
SPECT			
SSS	.6 ± .9	.3 ± .7	.037
SRS	.2 ± .6	.1 ± .6	.518
SDS	.4 ± .8	.2 ± .7	.061
Stress			
Bandwidth (°)	57 ± 35	43 ± 24	.006
Phase SD	16 ± 10	12 ± 7	.011
Rest			
Bandwidth (°)	53 ± 33	38 ± 22	.002
Phase SD	14 ± 10	10 ± 6	.003
Coronary risk, n (%)			
Hypertension	47 (87)	378 (68)	.004
Dyslipidemia	34 (63)	294 (53)	.164
Smoking	25 (46)	155 (28)	.005
Diabetes	19 (35)	140 (25)	.114
<b>(C)</b>	<b>With cardiac event (N = 20)</b>	<b>Without cardiac event (N = 290)</b>	<b>P value</b>
Age (years)	69 ± 11	63 ± 13	.050
Gender, male (%)	20 (100)	171 (59.0)	< .001
BMI (kg/m <sup>2</sup> )	25 ± 3	23 ± 3	.009

**Table 3** continued

(C)	With cardiac event (N = 20)	Without cardiac event (N = 290)	P value
<b>QGS</b>			
EDV (mL)	97 ± 27	83 ± 23	.032
ESV (mL)	37 ± 23	26 ± 13	.066
LVEF (%)	65 ± 11	70 ± 9	.048
<b>SPECT</b>			
SSS	1.0 ± .9	.3 ± .6	.003
SRS	.5 ± .8	.2 ± .5	.135
SDS	.6 ± .8	.1 ± .5	.024
<b>Exercise test</b>			
ECG positive, n (%)	11 (55)	48 (17)	< .001
Capacity, METs	5.7 ± 1.7	6.2 ± 1.8	.216
<b>Stress</b>			
Bandwidth (°)	62 ± 37	42 ± 21	.026
Phase SD	17 ± 12	12 ± 6	.040
<b>Rest</b>			
Bandwidth (°)	50 ± 29	37 ± 20	.061
Phase SD	14 ± 8	10 ± 5	.052
<b>Coronary risk, n (%)</b>			
Hypertension	15 (75)	149 (51)	.041
Dyslipidemia	12 (60)	147 (51)	.420
Smoking	14 (70)	115 (40)	.008
Diabetes	11 (55)	70 (24)	.002

BMI, body mass index; ECG, electrocardiogram; EDV, end diastolic volume; ESV, end systolic volume; LVEF, left ventricular ejection fraction; METs, metabolic equivalents; QGS, quantitative-gated SPECT; SDS, summed differential score; SPECT, single-photon emission computed tomography; SRS, summed rest score; SSS, summed stress score

failure, the severity of LVMD increases in accordance with dobutamine stress, and a good response of CRT was achieved in patients with LVMD induced by dobutamine.<sup>17</sup> Regardless of adenosine, dobutamine increases oxygen demand of the myocardium via β1 stimulation and causes cardiac ischemia in patients with CAD. Accordingly, LVMD induced by dobutamine may be via to the same mechanism as that by exercise stress.

Previous reports showed that LVMD had an association with cardiac function.<sup>18</sup> In multivariate analysis of our study, bandwidth at rest was one of the independent predictors of cardiac events in global patients ( $P = .013$ ). Although in our study MPS had no signs of cardiac ischemia ( $SSS < 3$ ) and mean LVEF was within normal range ( $71 \pm 11\%$ ), LVEF was significantly smaller ( $P < .001$ ) and SSS was significantly greater ( $P < .001$ ) in patients with MCEs (Table 3A). A reduced LVEF and severity of myocardial scar on SPECT imaging were reported to be independent predictors of LVMD.<sup>19</sup> Accordingly, it was natural that bandwidth at rest also had the ability as a predictor for future cardiac events, similarly to LVEF or SSS.

MPS has been established as a tool to diagnose CAD, but in contrast to the other morphological

approaches, such as coronary angiography or computed tomography, exercise or pharmacological stress is necessary for an accurate diagnosis of CAD. Although pharmacological stress is considered when patients have a low exercise tolerance, MPS by pharmacological stress is known to have the same sensitivity and specificity for the diagnosis of CAD as exercise stress.<sup>20,21</sup> Pharmacological stress patients had a higher mortality rate than exercise stress patients even though they had no evidence of cardiac ischemia based on stress MPS<sup>22</sup> because they were older, and had a higher prevalence of diabetes and hypertension. In our study, pharmacological stress patients were also older ( $P < .001$ ), had a lower eGFR ( $P = .004$ ), and higher prevalence of hypertension ( $P < .001$ ), but there was no significant difference in cardiac events between pharmacological and exercise stress SPECT ( $P = .108$ , Figure 1). One of the reasons may be that patients were classified as low-cardiac risk based on MPS. All patients had no evidence of cardiac ischemia on MPS ( $SSS < 3$ ). The annual event rate for cardiac events was reported to be low in patients with a normal scan.<sup>8,23</sup> As mortality is influenced by other clinical factors, such as age, gender, or

**Table 4.** Univariate and multivariate analysis for cardiac events in global patients (A), pharmacological (B) and exercise (C) stress groups

	Univariate			Multivariate		
	Hazard ratio	Confidence interval	P value	Hazard ratio	Confidence interval	P value
<b>(A)</b>						
Age	1.046	1.021-1.072	< .001	1.051	1.024-1.079	< .001
Gender, male	3.020	1.736-5.254	< .001	1.021	1.021-3.649	.043
QGS LVEF	.961	.947-.975	< .001	.971	.953-.990	.003
SPECT SSS	1.769	1.379-2.271	< .001	1.464	1.127-1.902	.004
Rest bandwidth	1.015	1.007-1.023	< .001	1.002	1.002-1.019	.013
Coronary risk						
Hypertension	2.911	1.533-5.528	.001	1.575	.807-3.075	.183
Dyslipidemia	1.289	.801-2.073	.296	1.152	.697-1.903	.582
Smoking	2.218	1.400-3.513	< .001	1.737	1.027-2.939	.039
Diabetes	1.134	.940-1.368	.188	.972	.748-1.263	.829
<b>(B)</b>						
Age	1.053	1.019-1.087	.002	1.054	1.019-1.090	.002
QGS LVEF	.947	.926-.969	< .001	.967	.950-.985	< .001
SPECT SSS	1.511	1.113-2.052	.008	1.263	.919-1.734	.150
Stress bandwidth	1.013	1.004-1.022	.004	1.007	.998-1.016	.117
Coronary risk						
Hypertension	2.758	1.246-6.104	.012	1.884	.834-4.255	.128
Dyslipidemia	1.15	.661-2.000	.621	1.071	.600-1.912	.816
Smoking	2.102	1.231-3.589	.007	1.977	1.132-3.455	.017
Diabetes	1.105	.830-1.472	.495	1.042	.704-1.542	.838
<b>(C)</b>						
Age	1.031	.989-1.075	.147	1.034	.982-1.089	.202
QGS LVEF	.94	.895-.987	.013	.97	.930-1.011	.148
SPECT SSS	2.667	1.674-4.250	< .001	2.459	1.461-4.141	< .001
Stress bandwidth	1.02	1.007-1.034	.002	1.017	1.003-1.032	.019
Coronary risk						
Hypertension	2.81	.931-8.478	.067	1.357	.400-4.602	.625
Dyslipidemia	1.487	.585-3.778	.404	.945	.321-2.787	.919
Smoking	3.818	1.374-10.607	.010	5.343	1.708-16.718	.004
Diabetes	1.202	.927-1.560	.165	.923	.643-1.326	.665

LVEF, left ventricular ejection fraction; QGS, quantitative-gated SPECT; SPECT, single-photon emission computed tomography; SSS, summed stress score

renal function, age was an independent predictor in pharmacological stress patients in our study.

**Limitations**

First, this study was a retrospective, non-randomized study. The patients who had pharmacological stress were significantly older because of their lower physical

activity. Age has a strong impact on the prognosis of elderly people. The cardiac event rate did not differ between the exercise and pharmacological stress groups. If the patients with pharmacological stress were younger, the cardiac event rate may have been lower in our study cohort. Therefore, LVMD is less likely to be an independent predictor in patients with pharmacological stress. Second, in this study, coronary intervention



due to acute coronary syndrome or worsening symptom of angina included major cardiac events because all patients had no evidence of cardiac ischemia on MPS. Thus, the cardiac event rate was higher (8.1%) than that in previous reports. Third, Cox proportional regression analysis could not be employed for multivariate analysis with gender as a variable in separate groups because the number of cardiac events was relatively low and especially in exercise stress group all patients with events were male. Bandwidth at stress had significant strong correlations with that at rest both in exercise ( $r = .985, P < .001$ ) and pharmacological stress ( $r = .986, P < .001$ ). For these reasons bandwidth at rest could not be added to the variables at both exercise and pharmacological stress groups. When bandwidth at rest was included as variables instead of that at stress, it was not an independent predictor both in exercise ( $P = .0644, CI .999$  to  $1.036$ ) and pharmacological ( $P = .109, CI .998$  to  $1.016$ ) stress. Thus, the indices of LVMD at stress might be more useful as a prognostic marker than those at rest, especially in exercise stress.

### New Knowledge Gained

Each index of the phase analysis of exercise stress MPS was related to cardiac events even though MPS demonstrated no evidence of cardiac ischemia. Pharmacological stress is suitable for elderly patients who have a low exercise tolerance, but the information provided by exercise stress is greater than that by pharmacological stress in the clinical setting.

### CONCLUSIONS

LVMD induced by exercise stress was an independent predictor of cardiac events in patients with normal perfusion SPECT, whereas that induced by pharmacological stress had no association with further events.

### Disclosures

*Drs Tomohiko Sakatani, Takeru Kasahara, Daisuke Irie, Yoshinori Tsubakimoto, Akiko Matsuo, Hiroshi Fujita, Keiji Inoue have no conflicts of interest to declare.*

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