Prognostic Value of Left Ventricular Dyssynchrony Assessed with Nuclear Cardiology in Patients with Known or Suspected Stable Coronary Artery Disease with Preserved Left Ventricular Ejection Fraction

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Summary

Left ventricular (LV) mechanical dyssynchrony assessed with phase analysis of electrocardiogram (ECG)-gated single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is useful for predicting major cardiac events (MCEs) in patients with cardiac dysfunction. However, there is no report on its usefulness in Japanese patients with known or suspected stable coronary artery disease (CAD) with preserved LV ejection fraction (LVEF).

We retrospectively investigated 3,374 consecutive patients with known or suspected CAD who underwent rest 201Tl and stress 99mTc-tetrofosmin ECG-gated SPECT MPI and had preserved LVEF (≥ 45%), and followed them up to confirm their prognosis for three years. The composite endpoint was the onset of MCEs consisting of cardiac death, non-fatal myocardial infarction (MI), unstable angina pectoris, and severe heart failure requiring hospitalization. LV mechanical dyssynchrony was evaluated with phase analysis with the Heart Risk View-F software to obtain the phase bandwidth and standard deviation.

During the follow-up, 179 patients experienced MCEs: cardiac death (n = 42); non-fatal MI (n = 34); unstable angina pectoris (n = 54); and severe heart failure (n = 49). Results of the multivariate analysis showed age, a history of MI, diabetes mellitus, summed stress score, and stress phase bandwidth to be independent predictors for MCEs. In Kaplan-Meier analysis, prognoses were significantly stratified with the tertiles of stress phase bandwidth.

LV mechanical dyssynchrony assessed with ECG-gated SPECT MPI is useful for predicting a prognosis and stratifying the risk of MCEs in Japanese patients with known or suspected stable CAD with preserved LVEF.

Key words: Cardiac outcome, Risk stratification, Phase analysis, Gated single photon emission computed tomography, Ischemia

Left ventricular (LV) mechanical dyssynchrony, which is frequently observed in patients with a cardiac dysfunction, is a very important prognostic factor in patients with cardiac disease. These days, a phase analysis has been available on electrocardiogram (ECG)-gated myocardial perfusion single photon emission computed tomography (SPECT) to evaluate indices of LV mechanical dyssynchrony as well as those of LV systolic functions.1,2)

The LV mechanical dyssynchrony indices, including heart failure,3,4) implantable cardioverter-defibrillator/cardiac resynchronization therapy with a defibrillator,5) and non-ischemic cardiomyopathy, derived from phase analysis have been reported to have diagnostic and prognostic values in patients with LV dysfunction.6) Besides, there have been only a few reports demonstrating the diagnostic and prognostic values of LV mechanical dyssynchrony indices in patients with coronary artery disease (CAD). Besides, those were results from small-scale studies,7,8) and there is no report on prediction and risk stratification of future cardiac events with LV mechanical dyssynchrony indices derived from phase analysis on the gated SPECT in Japanese patients.

Generally, depending on infarct size, LV mechanical dyssynchrony that is observed in patients with ischemic cardiac dysfunction is considered to have a poor prognosis.9) However, it is known that LV mechanical dyssynchrony is also observed in patients with normal LV systolic function.10) Therefore, it still remains unclear what is a predictor for LV mechanical dyssynchrony or how LV
mechanical dyssynchrony is associated with a prognosis of CAD in patients with known or suspected stable CAD with preserved LV ejection fraction (LVEF).

Stress phase bandwidth as an LV mechanical dyssynchrony index has been reported to be high in patients with multivessel CAD possibly underestimated by SPECT, even though they had preserved LVEF. We therefore postulated that the prognoses in CAD patients, but with the exception of myocardial ischemia and LVEF, with preserved LVEF might be influenced by cardiac indices. This study is a single-center, large-scale retrospective prognostic study using nuclear cardiology in Japanese patients with known or suspected stable CAD with preserved LVEF in order to demonstrate an association between LV mechanical dyssynchrony indices and future major cardiac events (MCEs) and the potential of the indices for risk stratification of MCEs.

**Methods**

**Patient population:** We retrospectively investigated 3,374 consecutive patients with known or suspected CAD who underwent rest 201Tl and stress 99mTc-tetrofosmin ECG-gated SPECT myocardial perfusion imaging (MPI) at the Nihon University Itabashi Hospital between April 2009 and August 2015 and who had preserved LVEF (≥ 45%). We followed up the patients to confirm their prognosis for three years. We excluded patients aged ≤ 20 years, those with hypertrophic or dilated cardiomyopathy, those with serious valvular heart disease, those with acute coronary syndromes within three months, those undergoing revascularization within three months before and after the SPECT, those with non-sinus rhythm, those having a history of cardiac resynchronization therapy (CRT), and those with left bundle branch block. A patient follow-up was performed with their medical records and completed for 3,191 (94.6%) of the patients. Consequently, data from the 3,191 patients were retrospectively analyzed.

This study was approved by the institutional review board of Nihon University Itabashi Hospital.

**ECG-gated SPECT MPI:** The procedure of rest 201Tl and stress 99mTc-tetrofosmin ECG-gated SPECT MPI was performed according to a previously reported protocol. All patients received an intravenous (i.v.) injection of 201Tl (111 MBq) and a 16-frame gated SPECT MPI was initiated 10 minutes after injection during rest. In 25% of the patients, the i.v. injection of 99mTc-tetrofosmin (740 MBq) was then performed under stress induced by ergometer exercise, or in 75% of the patients by injection of adenosine triphosphate. Sixteen-frame gated SPECT MPI acquisition was initiated 30 minutes after the exercise or 30 to 60 minutes after the adenosine stress. The acquisition was performed in a supine position and subsequently in a prone position. No attenuation or scatter correction was used. A 12-lead ECG was monitored continuously during stress tests. The heart rate and blood pressure were recorded at baseline and every minute for at least 3 minutes after the stress.

The projection data over 360° were obtained with 64 × 64 matrices and a circular orbit. A triple-detector SPECT MPI system equipped with low-energy high-resolution collimators was used (GCA9300A; Canon Medical Systems Corp., Tokyo, Japan). SPECT MPI scans were reconstructed from the data with a data processor (JETStream Workspace 3.0; Philips North America, Milpitas, CA, USA) combined with a Butterworth filter of 201Tl (order 5; cut-off frequency 0.42 cycles/cm), a Butterworth filter of 99mTc (order 5; cut-off frequency 0.44 cycles/cm), and a ramp filter.

**SPECT MPI interpretation:** The SPECT MPI scans were divided into 20 segments on three short-axis slices (distal, mid, basal) and one vertical long-axis (mid) slice, and the tracer uptake of each segment was visually scored using a 5-point scale (0: normal; 1: slight reduction in the uptake; 2: moderate reduction in the uptake; 3: severe reduction in the uptake; and 4: absence of the uptake). The sum total of the scores of 20 segments in the stress and rest images provided the summed stress score (SSS) and summed rest score (SRS), respectively. The summed difference score (SDS) was calculated as the difference between the SSS and SRS. The visual semi-quantitative scoring was performed by two independent expert interpreters who were not provided with the patients’ clinical data. Cohen’s kappa (k), which was calculated to determine the inter-observer variability for the summed defect score, was 0.90, indicating very good reproducibility.

**LV functional analysis with ECG-gated SPECT MPI:** Sixteen-frame quantitative gated SPECT data were analyzed with the Heart Risk View-F software (Nihon Medi-Physics, Tokyo, Japan) to calculate the LVEF (%), LV end-diastolic volume (LVEDV, mL), and LV end-systolic volume (LVESV, mL). LV mechanical dyssynchrony was evaluated with the phase histogram and phase map of the onset of myocardial contraction derived from the phase analysis of the Heart Risk View-F software. The histogram analysis provided standard deviation of the phase distribution (phase SD) and 95% width of the histogram (Phase bandwidth) was calculated. Figure 1 illustrates representative phase histograms and phase map images in a normal case (Figure 1A) and in a case with severe LV mechanical dyssynchrony (Figure 1B). Phase bandwidth and SD were 17.00 and 4.98, respectively, in the normal case and 121.00 and 43.15, respectively, in the case with severe LV mechanical dyssynchrony.

**Patient follow-up:** All patients were followed up for three years (37.2 ± 8.4 months) after the initial stress ECG-gated SPECT MPI.

The primary endpoint was the onset of MCEs, which was a composite of cardiovascular death, non-fatal myocardial infarction (MI), unstable angina pectoris (UAP), and severe heart failure requiring hospitalization during the follow-up.

Cardiac death was defined as death due to any cardiac cause, including fatal MI, heart failure, and sudden cardiac death. For a patient who required unscheduled hospitalization for the management of UAP, occurring within 24 hours of the most recent symptoms, and who had worsening ischemic discomfort, ischemic ECG changes without ST elevation, and negative troponins, a diagnosis of UAP was provided. For a patient who required unscheduled hospitalization for the management of
acute heart failure and who had chest X-ray findings attributable to cardiac dysfunction (pulmonary edema, etc.) and respiratory distress, a diagnosis of severe heart failure requiring hospitalization was provided. A patient who had insufficient data indicating the occurrence of the MCEs was regarded as a non-event case.

When a patient had several MCEs, only the first event was set as the follow-up endpoint.

Statistical analysis: Continuous variables were calculated as means and SDs. Intergroup comparisons of continuous variables were achieved with a one-way analysis of variance for three groups (Table I) and an independent t-test for two groups (Table IV). Intergroup comparisons of categorical variables were achieved with the chi-square test (Tables I, IV, Figure 2).

Univariate and multivariate logistic models were employed to estimate predictors for the third tertile of stress phase bandwidth (Table II). The chi-square for trend test was used to compare baseline characteristics of patients and MCE rates during the three-year follow-up between tertiles of stress phase bandwidth. (Table III). A Cox proportional hazards model was used for univariate analyses to identify significant predictors of MCEs. A stepwise Cox proportional hazards model was employed for multivariate analyses with significant predictors as variables in order to determine independent predictors of MCEs (Table V). The goodness of fit using global chi-square values by combination of independent predictors of MCEs was achieved with the chi-square test (Figure 3).

The Kaplan-Meier survival analysis was used to estimate MCE-free survivals in each tertile of stress phase bandwidth. A log-rank test was used to analyze the homogeneity of the survival curves between tertiles of stress phase bandwidth (Figure 4).

All data were analyzed with the MedCalc Software program, Version 18.5 (MedCalc Software, Mariakerke, Belgium). A P-value of < 0.05 was considered statistically significant.

Results

Baseline characteristics of patients: Table I summarizes baseline characteristics of the patients in each tertile of the stress phase bandwidth. The number of the patients in the first (stress phase bandwidth: 7° to 24°), second (25° to 36°), and third (37° to 166°) tertiles was 1,102, 1,079, and 1,010, respectively. A higher stress phase bandwidth was significantly associated with the following clinical comorbidity: male patients; a history of MI or revascularization; hypertension; diabetes mellitus; smoking; and medications including aspirin, statins, β-blockers, calcium channel blockers, nitrates, angiotensin II receptor blockers.
showed hypertension, diabetes mellitus, SSS, stress LVEF. Among those, the result of the multivariate analysis predictors of the third tertile of stress phase bandwidth. In the gated SPECT MPI finding, a higher LVEF, and lower rest and stress phase bandwidth was significantly associated with a significant upward trend in the incidence of non-fatal heart failure death, and sudden cardiac death, between the tertiles of the stress phase bandwidth. However, there was a significant upward trend in the incidence of cardiovascular death, consisting of fatal MI, UAP, and severe heart failure requiring hospitalization (n = 49). Table III summarized MCE rates during three years in the patients in the first, second, and third tertiles of the stress phase bandwidth.

There was no statistically significant difference in the incidence of cardiovascular death, consisting of fatal MI, heart failure death, and sudden cardiac death, between the tertiles of the stress phase bandwidth. However, there was a significant upward trend in the incidence of non-fatal MI, UAP, and severe heart failure requiring hospitalization with an increasing stress phase bandwidth.

Table IV summarizes the background characteristics of the patients with and without MCEs. Proportions of the male patients, the older patients, and the patients who had a history of MI or revascularization and who had hypertension or diabetes mellitus were significantly higher in those patients with MCEs than in those patients without MCEs (P < 0.05). Regarding the gated SPECT MPI find-

Table I. Baseline Patients’ Characteristics in Each Tertile of the Stress Phase Bandwidth

| Tertiles of stress phase bandwidth | 7°-24° (n = 1102) | 25°-36° (n = 1079) | 37°-166° (n = 1010) | P value |
|-----------------------------------|------------------|------------------|-------------------|--------|
| Male patients                     | 511 (46%)        | 737 (68%)        | 791 (78%)         | < 0.001|
| Age                               | 70 ± 10          | 69 ± 11          | 69 ± 11           | 0.012  |
| History of MI                     | 118 (11%)        | 234 (22%)        | 334 (33%)         | < 0.001|
| History of revascularization      | 280 (25%)        | 378 (35%)        | 459 (45%)         | < 0.001|
| Hypertension                      | 751 (68%)        | 842 (78%)        | 865 (86%)         | < 0.001|
| Diabetes mellitus                 | 256 (23%)        | 340 (32%)        | 426 (42%)         | < 0.001|
| Hyperlipidemia                    | 640 (58%)        | 639 (59%)        | 614 (61%)         | 0.205  |
| Smoking                           | 211 (19%)        | 253 (23%)        | 254 (23%)         | 0.001  |
| Aspirin                           | 462 (42%)        | 572 (53%)        | 662 (66%)         | < 0.001|
| Statins                           | 542 (49%)        | 562 (52%)        | 576 (57%)         | 0.001  |
| β-blockers                        | 236 (21%)        | 297 (28%)        | 401 (40%)         | < 0.001|
| Calcium channel blocker           | 580 (53%)        | 635 (59%)        | 617 (61%)         | 0.001  |
| Nitrates                          | 155 (14%)        | 168 (16%)        | 203 (20%)         | 0.001  |
| ARB                               | 432 (39%)        | 537 (49%)        | 559 (55%)         | < 0.001|
| ACE Inhibitors                    | 59 (5%)          | 81 (8%)          | 103 (10%)         | < 0.001|
| SSS                               | 0.7 ± 2.3        | 2.3 ± 4.6        | 6.3 ± 8.5         | < 0.001|
| SRS                               | 0.2 ± 1.2        | 1.0 ± 3.2        | 4.0 ± 7.4         | < 0.001|
| SDS                               | 0.5 ± 1.8        | 1.2 ± 3.1        | 2.3 ± 4.0         | < 0.001|
| Rest LVEF (%)                     | 74.3 ± 6.7       | 71.5 ± 7.0       | 66.2 ± 9.1        | < 0.001|
| Rest LVEDV (mL)                   | 65.6 ± 19.2      | 75.7 ± 22.1      | 90.0 ± 30.5       | < 0.001|
| Rest LVESV (mL)                   | 16.9 ± 7.2       | 21.8 ± 9.7       | 31.6 ± 16.7       | < 0.001|
| Stress LVEF (%)                   | 72.5 ± 6.2       | 67.6 ± 6.9       | 60.4 ± 8.4        | < 0.001|
| Stress LVEDV (mL)                 | 70.0 ± 20.5      | 80.6 ± 22.8      | 96.2 ± 31.4       | < 0.001|
| Stress LVESV (mL)                 | 19.6 ± 8.8       | 26.7 ± 11.6      | 39.4 ± 18.7       | < 0.001|
| ΔLVEF (%)                         | 1.7 ± 6.1        | 3.9 ± 5.8        | 5.8 ± 6.4         | < 0.001|
| Rest phase SD (°)                 | 8.5 ± 3.7        | 11.3 ± 5.0       | 15.8 ± 7.2        | < 0.001|
| Rest phase bandwidth (°)          | 30.8 ± 12.3      | 40.1 ± 15.4      | 55.0 ± 21.6       | < 0.001|
| Stress phase SD (°)               | 5.1 ± 1.2        | 8.4 ± 1.2        | 15.2 ± 6.0        | < 0.001|
| Stress phase bandwidth (°)        | 18.5 ± 4.0       | 30.1 ± 3.4       | 52.7 ± 16.4       | < 0.001|

MI indicates myocardial infarction; ARB: angiotensin receptor blocker; ACE: angiotensin converting enzyme; SSS: summed stress score; SRS: summed rest score; SDS: summed difference score; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; ΔLVEF: a difference between rest and stress LVEF; and SD: standard deviation.

or angiotensin converting enzyme inhibitors (P < 0.05).

Similarly, in the gated SPECT MPI finding, a higher stress phase bandwidth was significantly associated with progressively higher SSS, SRS, SDS, rest and stress LVEDV and LVESV, and ΔLVEF, and lower rest and stress LVEF (P < 0.001).

In a comparison of LV mechanical dyssynchrony indices obtained from phase analysis between the tertiles, significant differences were found in rest and stress phase SDs and bandwidths. There was a significant upward trend in those indices with an increasing stress phase bandwidth (P < 0.001).

Predictors of the third tertile of stress phase bandwidth: Table II summarizes the results of univariate and multivariate logistic regression analyses for evaluating a predictor for the third tertile of stress phase bandwidth. All clinical comorbid variables, namely age, male patients, a history of MI or revascularization, hypertension, diabetes mellitus, smoking, SSS, SRS, SDS, rest and stress LVEF, LVEDV, and LVESV, and ΔLVEF, were significant predictors of the third tertile of stress phase bandwidth. Among those, the result of the multivariate analysis showed hypertension, diabetes mellitus, SSS, stress LVEF, and stress LVESV to be independent predictors of the third tertile of stress phase bandwidth.

MCE rates: During the follow-up, 179 (5.6%) of 3,191 patients experienced MCEs consisting of cardiovascular death (n = 42), non-fatal MI (n = 34), UAP (n = 54), and severe heart failure requiring hospitalization (n = 49). Table III summarized MCE rates during three years in the patients in the first, second, and third tertiles of the stress phase bandwidth.

There was no statistically significant difference in the incidence of cardiovascular death, consisting of fatal MI, heart failure death, and sudden cardiac death, between the tertiles of the stress phase bandwidth. However, there was a significant upward trend in the incidence of non-fatal MI, UAP, and severe heart failure requiring hospitalization with an increasing stress phase bandwidth.
### Table IV. Background Characteristics of Patients with and without MCEs

|                  | MCE (+) | MCE (−) | P value |
|------------------|---------|---------|---------|
| Male patients    | 179     | 3012    | 0.0291  |
| Age (years)      | 72 ± 10 | 69 ± 11 | <0.0001 |
| History of MI    | 76 (42%)| 610 (20%)| <0.0001 |
| History of revascularization | 100 (56%) | 1017 (34%) | <0.0001 |
| Hypertension     | 151 (84%)| 2307 (77%)| 0.0165  |
| Diabetes mellitus| 78 (44%)| 944 (31%)| 0.0007  |
| Smoking          | 48 (27%)| 670 (22%)| 0.1548  |
| Summed stress score | 7.2 ± 8.5 | 2.7 ± 5.8 | <0.0001 |
| Summed rest score | 4.2 ± 7.3 | 1.5 ± 4.6 | <0.0001 |
| Summed difference score | 3.1 ± 4.9 | 1.2 ± 3.0 | <0.0001 |
| Rest LVEF (%)    | 66.0 ± 9.7 | 71.1 ± 8.1 | <0.0001 |
| Rest LVEDV (mL)  | 86.6 ± 30.8| 76.1 ± 25.8| <0.0001 |
| Rest LVESV (mL)  | 31.1 ± 18.4| 22.7 ± 12.7| <0.0001 |
| Stress LVEF (%)  | 61.2 ± 9.4 | 67.4 ± 8.5 | <0.0001 |
| Stress LVEDV (mL)| 94.9 ± 31.4| 81.1 ± 26.9| <0.0001 |
| Stress LVESV (mL)| 38.7 ± 20.0| 27.7 ± 15.3| <0.0001 |
| ΔLVEF (%)        | 4.8 ± 6.9 | 3.7 ± 6.3 | 0.0230  |
| Rest phase SD (°)| 14.1 ± 7.2 | 11.6 ± 6.1 | <0.0001 |
| Rest phase bandwidth (°)| 49.3 ± 23.1 | 41.2 ± 19.1| <0.0001 |
| Stress phase SD (°)| 12.1 ± 7.2 | 9.2 ± 5.3 | <0.0001 |
| Stress phase bandwidth (°)| 42.4 ± 21.7 | 32.7 ± 16.7| <0.0001 |

MI indicates myocardial infarction; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; ΔLVEF: a difference between rest and stress LVEF; and SD: standard deviation.

Figure 2 shows overall MCE rates for three years in the patients in each tertile of the stress phase bandwidth. MCE rates for three years were 3.0%, 4.9%, and 9.1% in the first, second, and third tertiles of stress phase bandwidth, respectively. Overall MCE rates significantly rose with an increasing stress phase bandwidth. There was a statistically significant difference in the MCE rates between the tertiles of stress phase bandwidth (P < 0.05).

**Predictors for MCEs:** Table V summarizes the results of the univariate and multivariate Cox proportional hazards regression analyses used to identify a predictor for MCEs. Univariate significant predictors for MCEs were age, male gender, a history of MI or revascularization, hypertension, diabetes mellitus, SSS, SRS, SDS, rest and stress LVEF, LVEDV, and LVESV, ΔLVEF, and rest and stress phase SD and phase bandwidth. Among those, age, a history of MI, diabetes mellitus, SSS, and stress phase bandwidth were identified as multivariate independent predictors.

Figure 3 shows changes in global chi-square values for prediction of MCEs with combinations of the independent predictors identified with the multivariate analysis. The global chi-square values for MCE prediction were 20.8 for age, 32.2 for age and diabetes mellitus, 71.1 for age, diabetes mellitus, and a history of MI, 97.5 for age, diabetes mellitus, a history of MI, and SSS, and 110.7 for age, diabetes mellitus, a history of MI, SSS, and stress phase bandwidth. The global chi-square values significantly increased with the incremental number of independent predictors combined (P < 0.01).

**Prediction of MCEs based on tertiles of stress phase bandwidth:** Figure 4 illustrates Kaplan-Meier curves of
of an increase of the bandwidth results in a higher rate of stress phase bandwidth and the risk of future MCEs. A investigation in detail a correlation between the extent of had preserved LVEF. One of the study objectives was to ifying risk of MCEs in patients with known or suspected stress phase bandwidth assessed for LV mechanical second, and third tertiles of stress phase bandwidth (tertiles of stress phase bandwidth). The patients in the first tertile of stress phase bandwidth had the worst prognosis. The patients in the third tertile of stress phase bandwidth. In addition, according to results of the multivariate analysis, stress phase bandwidth and SSS as well as age, a history of MI, and diabetes mellitus were each an independent predictor of MCE risk. Therefore, adding SSS to the independent predictors of patient’s background factors improved the goodness of fit for the logistic regression model for predicting MCEs and further addition of stress phase bandwidth to those significantly improved the goodness. As mentioned above, the indices obtained from gated SPECT MPI have an important role in prognostic prediction, even in patients with known or suspected stable CAD with preserved LVEF.

Discussion

This is the first report in Japan, demonstrating that stress phase bandwidth assessed for LV mechanical dyssynchrony is useful for predicting prognosis and stratiﬁying risk of MCEs in patients with known or suspected stable CAD who underwent ECG-gated SPECT MPI and had preserved LVEF. One of the study objectives was to investigate in detail a correlation between the extent of stress phase bandwidth and the risk of future MCEs. A tertile analysis of stress phase bandwidth indicated more of an increase of the bandwidth results in a higher rate of MCEs during three years. Based on results of the Kaplan-Meier analysis showing signiﬁcant differences in prognosis between the tertiles of stress phase bandwidth, MCE risk was stratified with the stress phase bandwidth. In addition, according to results of the multivariate analysis, stress phase bandwidth and SSS as well as age, a history of MI, and diabetes mellitus were each an independent predictor of MCE risk. Therefore, adding SSS to the independent predictors of patient’s background factors improved the goodness of fit for the logistic regression model for predicting MCEs and further addition of stress phase bandwidth to those signiﬁcantly improved the goodness. As mentioned above, the indices obtained from gated SPECT MPI have an important role in prognostic prediction, even in patients with known or suspected stable CAD with preserved LVEF.

LV mechanical dyssynchrony is observed not only in patients with ischemic cardiac dysfunction but also in those with normal LV systolic function. However, it is as yet unclear whether the mechanism of the occurrence of LV mechanical dyssynchrony is associated with the oc-

| Table II. Univariate and Multivariate Predictors for the Third Tertile of Stress Phase Bandwidth |
|---------------------------------------------------------------|
| **Univariate analysis** | **Multivariate analysis** |
|---------------------------------------------------------------|
| **Odds ratio** | **95% CI** | **P value** | **Odds ratio** | **95% CI** | **P value** |
| Age | 0.9943 | 0.9875-1.0011 | 0.1016 | | | |
| Male patients | 2.7002 | 2.2735-3.2071 | <0.0001 | | | |
| History of MI | 2.5673 | 2.1577-3.0545 | <0.0001 | | | |
| History of revascularization | 1.9281 | 1.6530-2.2490 | <0.0001 | | | |
| Hypertension | 2.2020 | 1.8034-2.6887 | <0.0001 | 1.7426 | 1.3738-2.2102 | <0.0001 |
| Diabetes mellitus | 1.9399 | 1.6590-2.2683 | <0.0001 | 1.3625 | 1.1262-1.6482 | 0.0015 |
| Smoking | 1.2433 | 1.0343-1.4814 | 0.0149 | | | |
| SSS | 1.1466 | 1.1293-1.1641 | <0.0001 | 1.0539 | 1.0345-1.0737 | <0.0001 |
| SRS | 1.1820 | 1.1554-1.2092 | <0.0001 | | | |
| SDS | 1.1468 | 1.1189-1.1754 | <0.0001 | | | |
| Rest LVEF | 0.8975 | 0.8878-0.9073 | <0.0001 | | | |
| Rest LVEDV | 1.0302 | 1.0268-1.0335 | <0.0001 | | | |
| Rest LVESV | 1.0853 | 1.0769-1.0937 | <0.0001 | | | |
| Stress LVEF | 0.8525 | 0.8420-0.8632 | <0.0001 | 0.8938 | 0.8768-0.9111 | <0.0001 |
| Stress LVEDV | 1.0306 | 1.0273-1.0338 | <0.0001 | | | |
| Stress LVESV | 1.0816 | 1.0745-1.0899 | <0.0001 | 1.0202 | 1.0100-1.0305 | 0.0001 |
| ΔLVEF | 1.0831 | 1.0690-1.0973 | <0.0001 | | | |

CI indicates confidence interval; MI: myocardial infarction; SSS: summed stress score; SRS: summed rest score; SDS: summed difference score; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; and ΔLVEF: a difference between rest and stress LVEF.

| Table III. MCE Rates for Three Years in Each Tertile of Stress Phase Bandwidth |
|---------------------------------------------------------------|
| **Overall** | **Tertiles of stress phase bandwidth** |
| **(n = 3191)** | **7°-24° (n = 1102)** | **25°-36° (n = 1079)** | **37°-166° (n = 1010)** | **P value for trend** |
| **n %** | **n %** | **n %** | **n %** | **n %** |
| Cardiovascular death | 42 1.3 | 11 1.0 | 12 1.1 | 19 1.9 | 0.0785 |
| Fatal MI | 14 0.4 | 2 0.2 | 6 0.5 | 6 0.6 | 0.1433 |
| Heart failure death | 17 0.5 | 3 0.2 | 5 0.5 | 9 0.9 | 0.0522 |
| Sudden cardiac death | 11 0.3 | 6 0.5 | 1 0.1 | 4 0.4 | 0.5319 |
| Non-fatal MI | 34 1.1 | 7 0.6 | 7 0.6 | 20 2.0 | 0.0030 |
| UAP | 54 1.7 | 10 0.9 | 21 1.9 | 23 2.2 | 0.0140 |
| Severe heart failure requiring hospitalization | 49 1.5 | 6 0.5 | 13 1.1 | 30 3.0 | <0.0001 |
| Total | 179 5.6 | 34 3.0 | 53 4.9 | 92 9.1 | <0.0001 |

MCE indicates major cardiac event; MI: myocardial infarction; and UAP: unstable angina pectoris.
The top of each bar is the mean width; and SSS, summed stress score; MCE, major cardiac event; ΔLVEF: a difference between rest and stress LVEF; and SD: standard deviation.

### Table V. Univariate and Multivariate Predictors for MCEs

| Predictor                      | Hazard ratio | 95% CI          | P value | Hazard ratio | 95% CI          | P value |
|-------------------------------|--------------|-----------------|---------|--------------|-----------------|---------|
| Age                           | 1.0353       | 1.0193-1.0515   | < 0.0001| 1.0378       | 1.0214-1.0544   | < 0.0001|
| Male gender                   | 1.4395       | 1.0405-1.9914   | 0.0278  |              |                 |         |
| History of MI                 | 2.8062       | 2.0864-3.7744   | < 0.0001| 1.6344       | 1.1188-1.8669   | 0.0111  |
| History of revascularization  | 2.3931       | 1.7817-3.2144   | < 0.0001|              |                 |         |
| Hypertension                  | 1.6358       | 1.0929-2.4484   | 0.0168  |              |                 |         |
| Diabetes mellitus             | 1.6842       | 1.2534-2.2631   | 0.0005  | 1.3842       | 1.0264-1.8669   | 0.0331  |
| Hyperlipidemia                | 1.0723       | 0.7936-1.4489   | 0.6495  |              |                 |         |
| SSS                           | 1.0733       | 1.0575-1.0893   | < 0.0001| 1.0351       | 1.0103-1.0605   | 0.0054  |
| SRS                           | 1.0641       | 1.0456-1.0830   | < 0.0001|              |                 |         |
| SDS                           | 1.1143       | 1.0839-1.1455   | < 0.0001|              |                 |         |
| Rest LVEF                     | 0.9362       | 0.9219-0.9508   | < 0.0001|              |                 |         |
| Rest LVEDV                    | 1.0125       | 1.0078-1.0173   | < 0.0001|              |                 |         |
| Rest LVESV                    | 1.0315       | 1.0241-1.0390   | < 0.0001|              |                 |         |
| Stress LVEF                   | 0.9265       | 0.9116-0.9415   | < 0.0001|              |                 |         |
| Stress LVEDV                  | 1.0142       | 1.0101-1.0183   | < 0.0001|              |                 |         |
| Stress LVESV                  | 1.0284       | 1.0225-1.0344   | < 0.0001|              |                 |         |
| ΔLVEF                         | 1.0269       | 1.0032-1.0512   | 0.0261  |              |                 |         |
| Rest phase SD                 | 1.0474       | 1.0298-1.0653   | < 0.0001|              |                 |         |
| Rest phase bandwidth          | 1.0172       | 1.0110-1.0234   | < 0.0001|              |                 |         |
| Stress phase SD               | 1.0578       | 1.0416-1.0743   | < 0.0001|              |                 |         |
| Stress phase bandwidth        | 1.0228       | 1.0170-1.0287   | < 0.0001| 1.0115       | 1.0013-1.0605   | 0.0055  |

CI indicates confidence interval; MI: myocardial infarction; SSS: summed stress score; SRS: summed rest score; SDS: summed difference score; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; ΔLVEF: a difference between rest and stress LVEF; and SD: standard deviation.

Figure 3. Changes in global chi-square values for prediction of MCEs with combinations of the independent predictors. The independent predictors were age, a history of MI, DM, SSS, and SPBW, which were identified with the multivariate analysis. The numerical value on the top of each bar is the mean global chi-square. MI indicates myocardial infarction; DM, diabetes mellitus; MCE, major cardiac event; SPBW, stress phase bandwidth; and SSS, summed stress score.

In the patients with the ischemic events. Regarding post ischemic stunning, ≥ 5% reduction in LVEF at stress detected by gated SPECT MPI has been reported to be an important marker of severe multivessel CAD.14-20] Also, multivessel CAD patients have been known to have higher stress phase bandwidth.7) In addition, ΔLVEF was a significant predictor of the third tertile of stress phase bandwidth in the present study. Considering this, post ischemic stunning caused by severe ischemia induces regional wall motion abnormality, which might deteriorate LV mechanical dyssynchrony. Therefore, in the present study, it may be suggested that post ischemic stunning is associated with the occurrence of ischemic MCEs.

On the other hand, according to the design of the present study, severe heart failure requiring hospitalization observed in the present study may be a similar pathologic condition to heart failure with preserved LVEF (HFpEF). The mechanism of the occurrence of HFpEF is generally known to be influenced by diastolic dysfunction. Therefore, we speculate that diastolic dyssynchrony induced by ischemia leads to diastolic dysfunction, which results in LV mechanical dyssynchrony on the systolic phase and consequently heart failure might develop. Diastolic dyssynchrony detected by gated SPECT MPI has been reported to have a prognostic value in patients with non-ischemic cardiac dysfunction,21] but there is no report on patients with CAD. The software quantifying diastolic dyssynchrony indices, however, is not available now in Japan. If that software becomes available, we will investigate in details in a future study.

Pazhenkottil, et al. evaluated qualitatively the prognostic value of LV mechanical dyssynchrony detected with phase analysis of gated SPECT MPI, and reported occurrence of ischemic MCEs in patients with known or suspected stable CAD with preserved LVEF. As supplemental data to the present study, ΔLVEF (a difference between rest and stress LVEF) was significantly higher in patients (n = 102) with the ischemic events of fatal- or non-fatal MI or UAP than in those patients (n = 3,089) without any ischemic event (6.7 ± 6.6 versus 3.7 ± 6.3, P < 0.0001). Mean LVEF decreased by 5% or more at stress...
that independent multivariate predictors for cardiac events in patients with known or suspected CAD were LV mechanical dyssynchrony, perfusion defects, and two cardiovascular risk factors.\textsuperscript{25} The present study proved that the following are useful for predicting a prognosis in patients with known or suspected stable CAD with preserved LVEF: age; diabetes mellitus; a history of MI; quantitative SSS; and stress phase bandwidth. Also, the third tertile of the stress phase bandwidth associated with a poor prognosis was considered to result from addition of stress-induced ischemia and LVEF reduction to risk factors including hypertension and diabetes mellitus. Based on such findings and considered to deteriorate a prognosis, the stress phase bandwidth might be higher and higher following repeated ischemia with daily exertion in patients having coronary risks. LV mechanical dyssynchrony would be an extremely significant factor determining a prognosis. Therefore, it is desirable to perform a prospective multicenter study to evaluate prediction of a prognosis and risk stratification with LV mechanical dyssynchrony indices derived from phase analysis of gated SPECT MPI in patients with known or suspected CAD in future.

Regarding a treatment strategy in patients with stable CAD according to ischemic myocardium derived from gated SPECT MPI, Hachamovitch, \textit{et al.}\textsuperscript{23} and our previous study\textsuperscript{14} demonstrated that revascularization makes patients with $\geq 10\%$ ischemic myocardium experience a good prognosis, while optimal medical therapy is better in those with $<5\%$ ischemic myocardium. Because the patients enrolled in this study had known or suspected stable CAD with preserved LVEF, they had low SSS, SRS, and SDS derived from gated SPECT MPI (mean ischemic myocardium: $1.6\% \pm 4.0\%$). According to the results of the preceding studies, such patients having low ischemic volume are considered to be a population who may have a good prognosis following optimal medical therapy. However, results of the present study demonstrated that patients with higher stress phase bandwidth experienced a poor prognosis even if they had low ischemic myocardium. Therefore, revascularization should be positively indicated for patients having high stress phase bandwidth.

Appropriate coronary revascularization resulting in ischemic reduction improves global LV function and leads to a good prognosis in patients with stable CAD having significant ischemic myocardium.\textsuperscript{24-26} In the present study, the stable CAD patients with preserved LVEF having high stress phase bandwidth who also experienced a poor prognosis following optimal medical therapy are considered to include those patients with multivessel disease accompanied by balanced ischemia.\textsuperscript{7} Such patients, if receiving revascularization, could have improvement in LV mechanical dyssynchrony and a greater increase in LVEF, which may inhibit the occurrence of fetal arrhythmia, and finally, those are considered to result in improvement on their prognosis.

Quantitative Gated SPECT software (QGS; Cedars Sinai Medical Center, Los Angeles, CA, USA) is widely used in daily clinical practice to analyze LV functions.\textsuperscript{27} The lower normal limit of LVEF derived from QGS has been reported to be $45\%$\textsuperscript{28}, and stable CAD patients with LVEF $\geq 45\%$ are considered to have a generally good prognosis.\textsuperscript{15,29} On the other hand, Heart Risk View-F (Nihon Medi-Physics, Tokyo, Japan) employed in the present study is Japanese software for evaluation of LV functions. Nakae, \textit{et al.} reported an extremely high correlation ($r > 0.96$) of LVEDV, LVESV, or LVEF between Heart Risk View-F and QGS.\textsuperscript{10} Although the participants included in the present study were the patients having LVEF $\geq 45\%$, their prognoses were not uniformly good. Their prognoses were stratified with their stress phase bandwidths in the present study, which is a new finding being useful for clinical practice.

\textbf{Limitations of this study:} This observational study has several limitations because it was a retrospective, single-center investigation.

There was bias in the type of MCEs such as a low rate of cardiac death, because the study participants were patients with preserved LVEF ($\geq 45\%$).

We excluded patients who underwent revascularization within three months before and after SPECT. The study participants were patients with known or suspected CAD according to ischemic myocardium derived from gated SPECT MPI, Hachamovitch, \textit{et al.}\textsuperscript{23} and our previous study, such patients having low ischemic myocardium. 1.6\% $\pm$ 4.0\%. According to the results of the MCE-free study participants were patients with known or suspected stable CAD with preserved LVEF $\geq 45\%$.28) The present study proved that the stable CAD patients with preserved LVEF having high stress phase bandwidth who also experienced a poor prognosis following optimal medical therapy are considered to include those patients with multivessel disease accompanied by balanced ischemia.7 Such patients, if receiving revascularization, could have improvement in LV mechanical dyssynchrony and a greater increase in LVEF, which may inhibit the occurrence of fetal arrhythmia, and finally, those are considered to result in improvement on their prognosis.
stable CAD with preserved LVEF, who were generally the object of optimal medical therapy because they had a low ischemic volume.1423 Therefore, exclusion of patients undergoing early revascularization is considered to have little influence on the results of the present study. On the basis of LV mechanical dyssynchrony indices derived from phase analysis of gated SPECT MPI in CAD patients with preserved LVEF and reduced LVEF (< 45%), we are planning a study investigating an association between improvement in ischemia and stress phase bandwidth after treatment and prognoses.

There was also the potential for institutional bias in optimal treatment with medicine to prevent cardiovascular events because this was an observational single-center study.

We used 201Tl + 99mTc-tetrofosmin dual isotope SPECT to improve throughput like the preceding studies.2425 The dual isotope SPECT provides higher radiation exposure than 1-day 99mTc-tetrofosmin low dose-high dose SPECT.26 However, for evaluation of LV mechanical dyssynchrony, the phase SD was significantly larger in the low dose of 99mTc than in the high dose of it.27 Because the high dose tracer was used only at stress in this study, the difference in the protocols is considered not to affect the study results.

Conclusions

LV mechanical dyssynchrony assessed with ECG-gated SPECT MPI was useful for predicting a prognosis and stratifying the risk of MCEs in Japanese patients with known or suspected stable CAD who had preserved LVEF.

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Disclosure

Conflicts of interest: All authors declare that they have no conflict of interest.

References

1. Chen J, Garcia EV, Folks RD, et al. Onset of left ventricular mechanical contraction as determined by phase analysis of ECG-gated myocardial perfusion SPECT imaging: Development of a diagnostic tool for assessment of cardiac mechanical dyssynchrony. J Nucl Cardiol 2005; 12: 687-95.
2. Garcia EV, Faber TL, Cooke CD, Folks RD, Chen J, Santana C. The increasing role of quantification in clinical nuclear cardiology: The Emory approach. J Nucl Cardiol 2007; 14: 420-32.
3. Henneman MM, Chen J, Dibbits-Schneider P, et al. Can LV dyssynchrony as assessed with phase analysis on gated myocardial perfusion SPECT predict response to CRT? J Nucl Med 2007; 48: 1104-11.
4. Henneman MM, Chen J, Ypenburg C, et al. Phase analysis of gated myocardial perfusion single-photon emission computed tomography compared with tissue Doppler imaging for the assessment of left ventricular dyssynchrony. J Am Coll Cardiol 2007; 49: 1708-14.
5. Zafrir N, Bental T, Strasberg B, et al. Yield of left ventricular dyssynchrony by gated SPECT MPI in patients with heart failure prior to implantable cardioverter-defibrillator or cardiac resynchronization therapy with a defibrillator: Characteristics and prediction of cardiac outcome. J Nucl Cardiol 2017; 24: 122-9.
6. Goldberg AS, Allaies MC, Cerqueira MD, Jaber WA, Aljardou WA. Prognostic value of left ventricular mechanical dyssynchrony by phase analysis in patients with non-ischemic cardiomyopathy with ejection fraction 35-50% and QRS < 150 ms. J Nucl Cardiol 2014; 21: 57-66.
7. Hida S, Chikamori T, Tanaka H, et al. Diagnostic value of left ventricular dyssynchrony after exercise and at rest in the detection of multivessel coronary artery disease on single-photon emission computed tomography. Circ J 2012; 76: 1942-52.
8. Hess PL, Shaw LK, Fudim M, Iskandrian AE, Borges-Neto S. The prognostic value of mechanical left ventricular dyssynchrony defined by phase analysis from gated single-photon emission computed tomography myocardial perfusion imaging among patients with coronary heart disease. J Nucl Cardiol 2017; 24: 482-90.
9. Legallois D, Marie PY, Franken PR, Djaballah W, Agostini D, Manrique A. Comparison of the dyssynchrony parameters recorded with gated SPECT in ischemic cardiomyopathy according to their repeatability at rest and to their ability to detect a synchrony reserve under dobutamine infusion. J Nucl Cardiol 2018.
10. Bernheim AM, Nakajima Y, Pellikka PA. Left ventricular dyssynchrony in patients with normal ventricular systolic function referred for exercise echocardiography. J Am Soc Echocardiogr 2008; 21: 1145-9.
11. Yoda S, Nakanishi K, Tano A, et al. Major cardiac event risk scores estimated with gated myocardial perfusion imaging in Japanese patients with coronary artery disease. J Nucl Cardiol 2016; 67: 64-70.
12. Berman DS, Kiat H, Friedman JD, et al. Separate acquisition rest thallium-201/stress technetium-99m sestamibi dual-isotope myocardial perfusion single-photon emission computed tomography: A clinical validation study. J Am Coll Cardiol 1993; 22: 1455-64.
13. Makita A, Matsumoto N, Suzuki Y, et al. Clinical feasibility of simultaneous acquisition rest (99m)Tc/Stress (201)TI dual-isotope myocardial perfusion single-photon emission computed tomography with semiconductor camera. Circ J 2016; 80: 689-95.
14. Yoda S, Hori Y, Hayase M, et al. Correlation between early revascularization and major cardiac events demonstrated by ischemic myocardium in Japanese patients with stable coronary artery disease. J Cardiol 2018; 71: 44-51.
15. Nishimura T, Nakajima K, Kusuoka H, Yamashina A, Nishimura S. Prognostic study of risk stratification among Japanese patients with ischemic heart disease using gated myocardial perfusion SPECT: J-ACCESS study. Eur J Nucl Med Mol Imaging 2008; 35: 319-28.
16. Nakae I, Hayashi H, Matsumoto T, Mitsunami K, Horie M. Clinical usefulness of a novel program “Heart Function View” for evaluating cardiac function from gated myocardial perfusion SPECT. Ann Nucl Med 2014; 28: 812-23.
17. Nakajima K, Okuda K, Matsuo S, Kiso K, Kinuya S, Garcia EV. Comparison of phase dyssynchrony analysis using gated myocardial perfusion imaging with four software programs: Based on the Japanese Society of Nuclear Medicine working group normal database. J Nucl Cardiol 2017; 24: 611-21.
18. Hida S, Chikamori T, Tanaka H, et al. Diagnostic value of left ventricular function after stress and at rest in the detection of multivessel coronary artery disease as assessed by electrocardiogram-gated SPECT. J Nucl Cardiol 2007; 14: 68-74.
19. Emmett L, Iwanochko RM, Freeman MR, Barolet A, Lee DS, Husain M. Reversible regional wall motion abnormalities on ex-
exercise technetium-99m-gated cardiac single photon emission computed tomography predict high-grade angiographic stenoses. J Am Coll Cardiol 2002; 39: 991-8.

20. Sharir T, Bacher-Stier C, Dhar S, et al. Identification of severe and extensive coronary artery disease by postexercise regional wall motion abnormalities in Tc-99m sestamibi gated single-photon emission computed tomography. Am J Cardiol 2000; 86: 1171-5.

21. Wang C, Tang H, Zhu F, et al. Prognostic value of left-ventricular systolic and diastolic dyssynchrony measured from gated SPECT MPI in patients with dilated cardiomyopathy. J Nucl Cardiol 2018.

22. Pazhenkottil AP, Buechel RR, Husmann L, et al. Long-term prognostic value of left ventricular dyssynchrony assessment by phase analysis from myocardial perfusion imaging. Heart 2011; 97: 33-7.

23. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. Circulation 2003; 107: 2900-7.

24. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: Results from the clinical outcomes utilizing revascularization and aggressive drug evaluation (COURAGE) trial nuclear substudy. Circulation 2008; 117: 1283-91.

25. Hori Y, Yoda S, Nakanishi K, et al. Myocardial ischemic reduction evidenced by gated myocardial perfusion imaging after treatment results in good prognosis in patients with coronary artery disease. J Cardiol 2015; 65: 278-84.

26. Nanasato M, Matsumoto N, Nakajima K, et al. Prognostic impact of reducing myocardial ischemia identified using ECG-gated myocardial perfusion SPECT in Japanese patients with coronary artery disease: J-ACCESS 4 study. Int J Cardiol 2018; 267: 202-7.

27. Germano G, Kiat H, Kavanagh PB, et al. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. J Nucl Med 1995; 36: 2138-47.

28. Ababneh AA, Sciaccio RR, Kim B, Bergmann SR. Normal limits for left ventricular ejection fraction and volumes estimated with gated myocardial perfusion imaging in patients with normal exercise test results: Influence of tracer, gender, and acquisition camera. J Nucl Cardiol 2000; 7: 661-8.

29. Sharir T, Germano G, Kavanagh PB, et al. Incremental prognostic value of post-stress left ventricular ejection fraction and volume by gated myocardial perfusion single photon emission computed tomography. Circulation 1999; 100: 1035-42.

30. Gibbons RJ, Chatterjee K, Daley J, et al. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Chronic Stable Angina). J Am Coll Cardiol 1999; 33: 2092-197.

31. AlJaroudi W, Jaber WA, Cerqueira MD. Effect of tracer dose on left ventricular mechanical dyssynchrony indices by phase analysis of gated single photon emission computed tomography myocardial perfusion imaging. J Nucl Cardiol 2012; 19: 63-72.