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Original Article

Prognostic Significance of Left Ventricular Dyssynchrony Assessed with Nuclear Cardiology

for the Prediction of Major Cardiac Events after Revascularization

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Abstract

Objective: This retrospective study was aimed at determining whether or not stress phase bandwidth (SPBW), a left ventricular (LV) mechanical dyssynchrony index, predicts major cardiac events (MCEs) and stratifies the risk of those in patients with coronary artery disease (CAD) who undergo revascularization.

Methods: Patients were followed up to confirm the prognosis for at least one year. The SPBW was calculated by a phase analysis using the Heart Risk View-F software program. The composite endpoint was the onset of MCEs, consisting of cardiac death, non-fatal myocardial infarction, unstable angina pectoris, and severe heart failure requiring hospitalization.

Patients: The study subjects were 332 patients with CAD who underwent coronary angiography and revascularization after confirming ≥5% ischemia detected by rest ^{201}Tl and stress ^{99m}Tc-tetrofosmin electrocardiogram-gated single-photon emission computed tomography myocardial perfusion imaging.

Results: During the follow-up, 35 patients experienced MCEs of cardiac death ($n = 5$), non-fatal myocardial infarction ($n = 3$), unstable angina pectoris ($n = 11$), and severe heart failure requiring hospitalization ($n = 16$). A receiver operating characteristics analysis indicated that the optimal cut-off value of the SPBW was 52° for predicting MCEs, and the MCE rate was significantly higher in the patients with an SPBW >52° than in those with an SPBW ≤52°. Results of the multivariate analysis showed the SPBW and estimated glomerular filtration rate

to be independent predictors for MCEs. In addition, the cut-off value of the SPBW significantly

stratified the risk of MCEs according to the results of the Kaplan-Meier analysis.

Conclusion: Evaluating the SPBW before revascularization may help predict future MCEs in

patients with CAD who intended to undergo treatment.

Key words: prognosis, risk stratification, left ventricular mechanical dyssynchrony, gated

single photon emission computed tomography, revascularization

Introduction

The decision concerning therapeutic strategies to improve the prognosis in patients with stable

coronary artery disease (CAD) depends on the ischemic volume derived from myocardial

perfusion single-photon emission computed tomography (SPECT). However, the risk of major

cardiac events (MCEs) after revascularization is known to be unrelated to the severity of the

ischemic volume (mild, moderate, or severe) before treatment (1, 2). In contrast, ischemic

reduction according to SPECT performed before and after revascularization has been reported

to be an important predictor of the prognosis of patients with stable CAD (3–5). However, it is

practically difficult to perform management based on evidence that ischemic reduction predicts

the prognosis, as SPECT is not routinely performed in the chronic phase after treatment in daily

clinical practice for various reasons, including patient transfer to another hospital after

treatment, the patient's refusal, and financial issues. In addition, ischemic reduction is not a

variable that can predict the prognosis prior to revascularization.

Left ventricular (LV) mechanical dyssynchrony is a very important prognostic factor in

patients with cardiac disease. Recently, LV mechanical dyssynchrony indices were reportedly

derived from a phase analysis with electrocardiogram (ECG)-gated myocardial perfusion

SPECT (6, 7). The LV mechanical dyssynchrony indices derived from the phase analysis were

found to show prognostic value in patients with non-ischemic cardiomyopathy (8–10).

However, few reports have described the prognostic value of LV mechanical dyssynchrony in

patients with CAD (11), and there have been no reports on its value in Japanese patients with

CAD who have undergone revascularization.

We reported that the LV mechanical dyssynchrony index stress phase bandwidth was a

predictor independent of the ischemic volume evaluated with SPECT. This index was shown

to be useful for stratifying the risk of MCEs in patients with known or suspected stable CAD

who had a preserved LV ejection fraction (LVEF) and were indicated for optimal medical

therapy (12). Based on those findings, we hypothesized that the stress phase bandwidth could

also predict the prognosis in patients with CAD who underwent revascularization.

Given the above, we conducted a retrospective study to determine whether or not the

LV mechanical dyssynchrony index predicts MCEs and stratifies the risk of MCEs in patients

with CAD who undergo revascularization.

Methods

Patient population

The study subjects were 332 patients who (1) underwent rest ^{201}Tl and stress ^{99m}Tc-tetrofosmin ECG-gated SPECT myocardial perfusion imaging (MPI) (2, 5, 12−15) at Nihon University Itabashi Hospital between January 2010 and November 2016, (2) had significant stenosis and ≥75% narrowing of the coronary arterial diameter according to the American Heart Association classification detected by coronary angiography (CAG) performed after confirmation of ≥5% ischemia by the SPECT, and (2) subsequently received revascularization.

The patients were followed up to confirm their prognoses for at least one year after the revascularization procedure. The mean interval between SPECT and the CAG was 0.9 ± 1.1 months, and that between the CAG and revascularization was 0.4 ± 1.2 months. Performing revascularization against all coronary vessels with ischemia evidenced by SPECT was defined as complete revascularization.

We excluded patients ≤20 years old, those with hypertrophic or dilated cardiomyopathy, those with serious valvular heart disease, those with the onset of acute coronary syndromes within 3 months, those with a non-sinus rhythm, those with left bundle branch block, those with pacemakers or implantable cardioverter defibrillator implantation, and those with a history of cardiac resynchronization therapy.

Patient follow-up was performed via medical records and was completed for 315 (95%)

patients. Consequently, data from these 315 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 ^{201}Tl and stress ^{99m}Tc-tetrofosmin ECG-gated SPECT MPI was performed according to a previously reported protocol (2, 5, 12−15). All patients received an intravenous (i.v.) injection of ^{201}Tl (111 MBq), and a 16-frame gated SPECT MPI was initiated 10 minutes after injection during rest. The i.v. injection of ^{99m}Tc-tetrofosmin (740 MBq) was then performed under stress induced by ergometer exercise in 25% of the patients or by adenosine triphosphate in 75%. 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 three 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 ^{201}Tl (order 5; cut-off frequency 0.42 cycles/cm), another of ^{99m}Tc (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 (13) on 3 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 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 respective summed scores were converted to a percentage of the total myocardium (visual % myocardium). The visual % myocardium was derived from the summed score divided by the maximum potential score (4 × 20) and multiplied by 100. When the SDS was 8, the visual ischemic % myocardium was 10% (16). The visual semi-quantitative scoring was performed by two independent expert interpreters who were not provided with the patients' clinical information. Cohen's kappa (κ), which was calculated to determine the inter-observer variability for the summed defect score, was 0.92,

indicating very good reproducibility.

The determination of coronary arterial territories involved with perfusion defects on a polar map of SPECT MPI was based on the standard model recommended by the SPECT MPI guidelines of the American Society of Nuclear Cardiology (17).

The LV functional analysis with ECG-gated SPECT MPI

Sixteen-frame quantitative gated SPECT data were analyzed with the Heart Risk View-F software program (Nihon Medi-Physics, Tokyo, Japan) to calculate the LVEF (%), LV end-diastolic volume (LVEDV, mL), and LV end-systolic volume (LVESV, mL) (18). 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 program. The histogram analysis provided the standard deviation of the phase distribution (phase SD) and the 95% width of the histogram (phase bandwidth) (19). The LV mechanical dyssynchrony indices were estimated by two independent expert cardiologists who were not provided with the patients' clinical information. Cohen's kappa (κ) was 0.97, indicating very good reproducibility.

Figure 1 shows representative phase histograms and phase map images in patients with no LV mechanical dyssynchrony (A) and severe LV mechanical dyssynchrony (B). The phase bandwidth and SD were 14.00 and 3.94, respectively, in the patients without LV mechanical

dyssynchrony and 118.00 and 39.71, respectively, in the patients with severe LV mechanical

dyssynchrony.

Patient follow-up

All 315 patients were followed up for 28.2 ± 12.0 months after the revascularization procedure.

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. A diagnosis of UAP was provided for patients who required

unscheduled hospitalization for the management of UAP occurring within 24 h of the most

recent symptoms and who had worsening ischemic discomfort, ischemic ECG changes without

ST elevation, and negative troponins. A diagnosis of severe heart failure requiring

hospitalization was provided for patients who required unscheduled hospitalization for the

management of acute heart failure and who had chest X-ray findings attributable to cardiac

dysfunction (e.g. pulmonary edema) and respiratory distress. 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 analyses

All continuous variables were calculated as the means and standard deviations, except for N-terminal prohormone of brain natriuretic peptide (NT-proBNP), which was expressed as the median and interquartile range, as it was markedly skewed. Intergroup comparisons of continuous were performed with an independent *t*-test. Intergroup comparisons of categorical variables were performed with the chi-square test.

Cohen's kappa (κ) was used to determine the inter-observer variability for the visual semi-quantitative scoring and LV mechanical dyssynchrony indices.

Univariate and multivariate logistic regression models were employed to estimate predictors for the high stress phase bandwidth (>52º). 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. The Kaplan-Meier survival analysis was used to estimate the MCE-free survival rate in patients grouped according to the best cut-off values of stress phase bandwidth for the prediction of MCEs calculated with a receiver operating characteristic analysis. A log-rank test was used to analyze the homogeneity of the survival curves between the groups.

All data were analyzed using the MedCalc Statistical software program, version 19.5.3 (Mariakerke, Belgium). A *P* value of <0.05 was considered statistically significant.

Results

Reproducibility of visual semi-quantitative scoring and LV mechanical dyssynchrony indices

Cohen's kappa (κ) was 0.92 for the summed defect score in the visual semi-quantitative scoring and 0.97 for 95% phase bandwidth in LV mechanical dyssynchrony indices, indicating very good reproducibility.

Cardiac event rates and best cut-off values of stress phase bandwidth

During the follow-up, 35 of 311 (11.3%) patients experienced MCEs consisting of cardiac death ($n = 5$), non-fatal MI ($n = 3$), UAP ($n = 11$), and severe heart failure requiring hospitalization ($n = 16$).

Figure 2 shows the receiver operating characteristic curve of stress phase bandwidth for detection of MCEs. The best cut-off value of stress phase bandwidth was 52°, with a sensitivity and specificity of 71% and 71%, respectively.

Baseline characteristics of patients

Table 1 summarizes the baseline characteristics of the patients divided into two groups according to the best cut-off value of stress phase bandwidth. The proportions of patients with a history of MI or revascularization, hypertension, and diabetes mellitus were significantly higher in the group with a high stress phase bandwidth than in that with a low stress phase

bandwidth. A greater proportion of patients with a high stress phase bandwidth received treatment with β-blockers or insulin than did those with a low stress phase bandwidth. The median NT-proBNP was significantly higher in the patients with a high stress phase bandwidth than in those with a low stress phase bandwidth (790 vs. 130 pg/mL; $P = 0.0006$). The patients with a high stress phase bandwidth had a significantly lower estimated glomerular filtration rate (eGFR) than did those with a low stress phase bandwidth (52.7 ± 24.8 vs. 63.5 ± 21.9 mL/min/1.73 m^2; $P = 0.0001$). In addition, the patients with a high stress phase bandwidth had a significantly larger QRS width than did those with a low stress phase bandwidth (107.3 ± 22.3 vs. 97.3 ± 15.6 ms; $P < 0.0001$).

The inter-group comparison of the visual % myocardium, cardiac function, angiographic findings, and MCE rates

Table 2 summarizes the visual % myocardium, cardiac function, angiographic findings, and MCE rates in the patients with low or high stress phase bandwidths. The patients with a high stress phase bandwidth had significantly higher values for the SSS%, SRS%, and SDS% than did those with a low stress phase bandwidth. The rest and stress LVEF were significantly lower in the patients with a high stress phase bandwidth than in those with a low stress phase bandwidth. The rest and stress LVEDV and LVESV were also significantly higher in the patients with a high stress phase bandwidth than in those with a low stress phase bandwidth.

The mean rest and stress phase SD were 13.1 and 9.5, respectively, in the patients with a low stress phase bandwidth and 27.2 and 25.3, respectively, in those with a high stress phase bandwidth. The mean rest and stress phase bandwidths were 47.3 and 33.8, respectively, in the patients with a low stress phase bandwidth and 85.6 and 82.5, respectively, in those with a high stress phase bandwidth.

The proportions of the patients with perfusion defects in left anterior descending artery (LAD) region were significantly higher in the group with a high stress phase bandwidth than in that with a low stress phase bandwidth (76% vs. 56%). The proportions of patients with perfusion defects in the left circumflex artery (LCX) region were significantly higher in the group with a high stress phase bandwidth than in that with a low stress phase bandwidth (51% vs. 30%). In contrast, there were no significant differences in the proportions of patients with perfusion defects in the right coronary artery (RCA) region between the groups (49% vs. 49%). The proportions of patients with three-vessel CAD and/or chronic total occlusion (CTO) vessels were significantly higher in the group with a high stress phase bandwidth than in that with a low stress phase bandwidth, while those with one-vessel CAD were significantly higher in the group with a low stress phase bandwidth than in that with a high stress phase bandwidth. The proportion of patients who underwent percutaneous coronary intervention (PCI) was significantly higher in the group with a low stress phase bandwidth than in that with a high stress phase bandwidth, but a greater proportion of patients with a high stress phase bandwidth

underwent coronary artery bypass grafting (CABG) than did those with a low stress phase

bandwidth.

The proportion of patients who underwent complete revascularization was significantly

higher in the group with a low stress phase bandwidth than in that with a high stress phase

bandwidth (87% vs. 73%; $P = 0.0016$), while there was no significant difference in the number

of patients undergoing repeat revascularization between the low and high stress phase

bandwidth groups (8% vs. 10%; $P = 0.4156$).

There was a significant difference in the MCE rates between the patients with a low

and high stress phase bandwidth (5% vs. 24%; p <0.0001). Among the overall MCEs, the

incidence of cardiac death or severe heart failure was significantly higher in the patients with

a high stress phase bandwidth than in those with a low stress phase bandwidth.

Association between coronary artery lesions and stress phase bandwidth

Figure 3 shows the coronary angiograms, polar map images, phase histograms, and phase maps

of three representative patients who had severe stenosis in the RCA proximal region (A), LAD

and LCX proximal regions (B), or LCX proximal region (C). Patient A had one-vessel disease

with ischemia in the inferior wall of his polar map images. His stress phase bandwidth was

26.00 at rest and 18.00 at stress. Patient B had two-vessel disease with infarct and ischemia in

the anterior wall and ischemia in the lateral wall of his polar map images. His stress phase

bandwidth was 92.00 at rest and 121.00 at stress. Patient C had one-vessel disease with ischemia in the inferolateral wall of his polar map images. His stress phase bandwidth was 44.00 at rest and 77.00 at stress.

Predictors of the high stress phase bandwidth (>52°)

Table 3 summarizes the results of univariate and multivariate logistic regression analyses for evaluating predictors of a high stress phase bandwidth (>52°). Significant predictors of a high stress phase bandwidth were a history of MI or revascularization, diabetes mellitus, higher NT-proBNP, SSS%, SRS%, SDS%, and rest and stress LVEDV and LVESV, and lower eGFR and rest and stress LVEF, perfusion defects in the LAD/LCX regions, three-vessel CAD, and CTO vessels. Among those variables, the multivariate analysis showed that the SRS%, stress LVEF, and perfusion defects in the LCX region were independent predictors of a high stress phase bandwidth (>52°).

Background characteristics of patients with and without MCEs

Table 4 summarizes the background characteristics of the patients with and without MCEs. The proportion of patients with a history of MI or revascularization was significantly higher in those with MCEs than in those without MCEs (P <0.05). The percentage using β-blockers was significantly higher in the patients with MCEs than in those without MCEs (74% vs. 49%; P =

0.0047). The median NT-proBNP was significantly higher in the patients with MCEs than in those without MCEs (2,591 vs. 179 pg/mL; P <0.0001). The eGFR was significantly lower in the patients with MCEs than in those without MCEs (44.5 ± 29.5 vs. 61.8 ± 21.9 mL/min/1.73 m^2; P <0.0001). Regarding the gated SPECT MPI findings, the patients with MCEs had significantly higher values for SSS%, SRS%, and rest and stress LVEDV and LVESV and lower values for rest and stress LVEF than those without MCEs (P <0.05). Similarly, the rest and stress phase SD and phase bandwidth were significantly higher in the patients with MCEs than in those without MCEs (P <0.0005).

The proportion of patients with MCEs who had perfusion defects in the LAD region was significantly higher than in those without MCEs (80% vs. 60%; P <0.05). There was no significant difference in the proportion of patients with perfusion defects in the RCA/LCX regions between those with and without MCEs.

Predictors for MCEs

Table 5 summarizes the results of univariate and multivariate Cox proportional hazards regression analyses for identifying predictors of MCEs. Univariate significant variables were a history of MI or revascularization, NT-proBNP, eGFR, SSS%, SRS%, rest and stress LVEF, LVEDV, and LVESV, rest and stress phase SD and bandwidth, and perfusion defects in the LAD region. Among those variables, the eGFR and stress phase bandwidth were identified as

multivariate independent predictors. higher SSS%, SRS% and SDS% before revascularization,

Prediction of MCEs based on stress phase bandwidth

Figure 4 shows the Kaplan-Meier curves of the MCE-free survival in patients with a low (≤52°)

or high (>52°) stress phase bandwidth. The patients with a high stress phase bandwidth had a

significantly worse prognosis than those with a low stress phase bandwidth.

Figure 5 shows the Kaplan-Meier curves of the MCE-free survival in patients with a

low (≤52°) or high (>52°) stress phase bandwidth who were divided by median SDS% into two

groups: the low ischemia group (A; SDS% ≤12.5%) and the high ischemia group (B; SDS%

>12.5%). The cut-off value (52°) of the stress phase bandwidth was able to significantly stratify

the risk of MCEs in the patients who had low or high ischemic % myocardium.

Discussion

Clinically useful and new findings

This is the first report demonstrating that stress phase bandwidth, a LV mechanical dyssynchrony index derived from the phase analysis of gated SPECT MPI before revascularization, is useful for the prediction and risk stratification of MCEs after treatment in Japanese patients with CAD. Patients with a high stress phase bandwidth before revascularization may have an extremely high risk of MCEs after treatment. The Kaplan-Meier analysis showed that the stress phase bandwidth stratified the risk of MCEs independently of ischemic volume before the treatment. In addition, the multivariate analysis showed that the stress phase bandwidth before the treatment was an independent predictor of MCEs. Therefore, the stress phase bandwidth derived from gated SPECT MPI is considered to play an important role in the prognostic prediction in CAD patients scheduled to undergo revascularization.

The ischemic volume before revascularization does not correlate with the incidence of MCEs after the treatment in patients with stable CAD (1, 2). Therefore, it is difficult to predict the prognosis in each patient based on his or her ischemic volume before revascularization. In contrast, a wide extent of phase bandwidth before revascularization is associated with an increased incidence of MCEs after the treatment in patients with stable CAD. Therefore, the phase bandwidth is clinically useful for identifying patients potentially at a high risk of MCEs after treatment. In particular, for patients with a high stress phase bandwidth before

revascularization, examinations such as SPECT should be performed to carefully monitor their clinical course in the chronic phase after the treatment. Such precise management will surely benefit patients.

Influence of the actual therapeutic strategies on the clinical outcome

We compared prognoses between the patients with low and high stress phase bandwidth. A significant difference in the proportion of patients with complete revascularization was noted between the low and high stress phase bandwidth groups (87% vs. 73%, $P = 0.0016$). In the low stress phase bandwidth group, the proportion of patients with one-vessel disease was high, and the number of patients with CTO vessels was small, which was associated with a high rate of complete revascularization. In contrast, a high proportion of patients had 3-vessel disease/CTO vessels in the high stress phase bandwidth group; however, 82% of those had undergone PCI, and a few had received CABG, which was associated with incomplete revascularization. Such differences in the revascularization strategy may affect the clinical outcome. However, it is impossible to perform complete revascularization against all ischemic vessels in patients who have multivessel disease with CTO lesions, which is associated with a higher stress phase bandwidth, as difficult PCI is required. Therefore, we should consider the application of optimal medical treatment, including CABG, in patients with a high stress phase bandwidth complicated with multivessel disease or CTO lesions.

Prediction of the post-treatment occurrence of MCEs by LV mechanical dyssynchrony before revascularization

The onset of LV mechanical dyssynchrony is associated with variations in the LV systolic phase caused by myocardial damage in patients with CAD, and the severity of LV mechanical dyssynchrony is known to be the greater in patients demonstrating ischemic cardiac dysfunction with a relatively large infarct size (20, 21). Sillanmäki et al. reported that LV mechanical dyssynchrony measured with SPECT was strongly associated with LV systolic dysfunction. The LVEF was shown to be the most powerful predictor for abnormal phase bandwidth, and its optimal cut-off value was 47% (sensitivity 73% and specificity 98%) (22). We also reported that the onset of LV mechanical dyssynchrony was associated with the occurrence of ischemic MCEs and related to post-ischemic stunning caused by a ≥5% reduction in the LVEF during stress in patients with known or suspected stable CAD and a preserved LVEF (12). Those findings suggest that a normalized LVEF after revascularization leads to improvement in LV mechanical dyssynchrony and ultimately a good prognosis. However, some patients with a high phase bandwidth before revascularization may experience only minor improvement in their LVEF, and their phase bandwidth may remain high, meaning that improvement in ischemia following revascularization is independent of that in the LVEF (5). Therefore, such patients are considered to have a high risk of cardiac death/heart failure and to

experience a poor prognosis. According to the present results, patients with a $\geq 52°$ stress phase bandwidth were predicted to be a high-risk population experiencing slight improvement in their LVEF after revascularization. This finding supports the notion that stress phase bandwidth may stratify the risk of MCEs after treatment. We have planned a study to evaluate the correlation between improvement in the stress phase bandwidth and the prognosis in patients who undergo revascularization.

The significance of the LV mechanical dyssynchrony evaluation for predicting MCEs after revascularization

The present findings show that stress phase bandwidth before revascularization is useful for predicting cardiac death and severe heart failure requiring hospitalization after treatment but not for predicting non-fatal MI and UAP. However, the results of our preceding large-scale study indicated that the stress phase bandwidth is also useful for predicting non-fatal MI and UAP (12). Therefore, the present results are attributed to the small number of patients experiencing non-fatal MI or UAP. More Japanese patients with severe CAD are hospitalized due to heart failure than acute coronary syndrome, including non-fatal MI and UAP (23). At 47%, the proportion of CAD is the highest among underlying disease in patients with heart failure requiring hospitalization, according to the JCS 2017/JHFS 2017 Guideline on the Diagnosis and Treatment of Acute and Chronic Heart Failure (24, 25).

Recently, PCI devices used for CAD patients have been improved, and there is great concern regarding the management of CAD patients with a high risk of heart failure, known as complex higher risk indicated patient (CHIP) (26). CHIPs are a population with complex lesions/coexisting disease who enjoy great benefit from revascularization. CHIPs are characterized by an advanced age; history of disease, including chronic kidney disease, stroke, or diabetes; CAD including left main and bifurcated disease; challenging plaque types, including calcified and long lesions; CTO; history of open-heart surgery; and low LVEF. The number of CHIPs is forecast to increase in the future. In the present study, CHIPs were probably included among the patients with a high stress phase bandwidth but not those with a low stress phase bandwidth before revascularization. Because the evaluation of the stress phase bandwidth can facilitate the identification of CHIPs and deciding whether or not cautious follow-up is required, such an evaluation is considered extremely important for clinical management.

Association between coronary artery lesions and stress phase bandwidth

In the present study, the proportion of patients with perfusion defects in the LAD or LCX region was significantly higher in those with a high stress phase bandwidth before revascularization than in those with low values, and the multivariate logistic regression analysis showed that perfusion defects in LCX region were an independent predictor of a high stress phase

bandwidth (>52°). In addition, perfusion defects in the LAD region, which tends to be the widest perfusion area, were a significant univariate predictor of MCEs. However, perfusion defects in the RCA region were not a significant predictor according to logistic regression analyses and Cox proportional hazards models.

Regarding the correlation between coronary lesions and LV dyssynchrony, Ng et al. reported that LV dyssynchrony parameters estimated with transthoracic echocardiograms were significantly higher in the presence of proximal LCX stenosis than in cases of other stenosis in patients with non-ST elevation myocardial infarction and that the presence of proximal LCX stenosis might delay mechanical activation of the LV free wall and induce LV dyssynchrony because the LCX normally supplies the LV lateral and posterior free walls that are finally activated by the cardiac conduction system (27). Although there are similarities between the present and those previous findings, the phase bandwidth derived from SPECT is highly reproducible compared with the LV dyssynchrony indices estimated with an echocardiogram (28, 29). No previous report has described the association between LV mechanical dyssynchrony and the myocardial hypo-perfusion area evaluated with ECG-gated SPECT MPI.

The comparison of our findings with those of previous studies

Predictors for MCEs in patients with CAD undergoing revascularization were evaluated in previous studies, including the COURAGE trial nuclear substudy (3), J-ACCESS 4 study (4),

and our preceding study (5). Ischemic reduction derived from SPECT data obtained before and after revascularization was found to be a significant predictor, and patients with ≥5% ischemic reduction had a better prognosis than those with <5% ischemic reduction. While ischemic reduction after revascularization is a significant predictor, its calculation requires data from SPECT performed before and after revascularization. In daily clinical practice, it is difficult to perform a re-examination with SPECT in many patients. Therefore, the patients who did not undergo the re-examination with SPECT have a demerit of failure to receive evidence-based management associated with prognostic prediction of nuclear cardiology.

In Japan, the assessment of functional ischemia with non-invasive imaging should be performed to decide revascularization in patients with stable CAD according to the revision of the medical service fees announced by the Ministry of Health, Labor, and Welfare in 2019 (www.mhlw.go.jp/content/12404000/000565821.pdf). Therefore, the evaluation of the stress phase bandwidth as well as the ischemic volume with SPECT before revascularization leads to not only decisions concerning the therapeutic strategy but also prognostic prediction and risk stratification, thereby resulting in better clinical management and benefit to patients. It is very rare for patients with a low stress phase bandwidth before revascularization to experience aggravation of LV mechanical dyssynchrony after the treatment, and such patients are basically considered to be a population with a good prognosis. Therefore, it is not necessary to estimate ischemic reduction with SPECT in the chronic phase after revascularization in patients with a

low stress phase bandwidth. However, it is necessary to perform SPECT in the chronic phase

after revascularization in order to evaluate ischemic reduction in patients with a high stress

phase bandwidth, as these patients have an increased incidence of MCEs after treatment. The

identification of high-risk patients among those with CAD requiring revascularization leads to

appropriate management in the chronic phase after treatment and is also useful from a medical

economy perspective. Therefore, in the future, a prospective multicenter study should verify

the usefulness of the combined ischemic volume and LV mechanical dyssynchrony.

Limitations

This observational study has several limitations because it was a retrospective, single-center,

investigation. Furthermore, its relatively small sample size may have led to bias in the type of

MCE. In addition, the study subjects included many patients (66%) with multi-vessel disease

in whom perfusion defects existed in ≥2 coronary arterial territories. Therefore, it was difficult

to directly compare the stress phase bandwidth estimated in each region of the coronary artery

between the LAD, RCA, and LCX. There was also potential institutional bias in the optimal

treatment with medicine to prevent cardiovascular events, as this was an observational single-

center study. In the present study, ^{201}Tl $+ ^{99m}$Tc-tetrofosmin dual isotope SPECT was used to

achieve improvement in the throughput, as in preceding studies (2, 5, 12–15). Dual-isotope

SPECT leads to higher radiation exposure than one-day ^{99m}Tc-tetrofosmin low dose-high dose

SPECT (30). In addition, it was difficult to directly compare the LV mechanical dyssynchrony index at rest and under stress because of differences in the tracers used between the two conditions. However, in our assessment of LV mechanical dyssynchrony, the low dose of ^{99m}Tc was reported to result in a significantly higher phase SD than the high dose (31). Therefore, we used the high-dose tracer only during stress in the present study. The difference in the protocols is considered not to have influenced the study results.

Conclusion

Evaluating the stress phase bandwidth assessed with ECG-gated SPECT MPI before revascularization may help predict future MCEs in patients with CAD scheduled to undergo such treatment.

Disclosures

All authors declare that they have no conflicts of interest.

References

1. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, BermanDS. 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: 2900–6.

2. 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.

3. 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.

4. 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.

5. 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.

6. 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.

7. 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.

8. Henneman MM, Chen J, Dibbets-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.

9. 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.

10. Goldberg AS, Alraies MC, Cerqueira MD, Jaber WA, Aljaroudi 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.

11. 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.

12. Hatta T, Yoda S, Hayase M, et al. 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. Int Heart J 2020; 61: 685–94.

13. Berman DS, Kiat H, Friedman JD, et al. Separate acquisition rest thalium-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.

14. Hayase M, Yoda S, Hatta T, et al. Prognostic Significance of the Residual SYNTAX Score and Ischemic Reduction Detected with Nuclear Cardiology for Prediction of Major Cardiac Events after Revascularization. Intern Med 2020 ; 59: 1361–71

15. Makita A, Matsumoto N, Suzuki Y, et al. Clinical Feasibility of Simultaneous Acquisition Rest (99m)Tc/Stress (201)Tl Dual-Isotope Myocardial Perfusion Single-Photon Emission Computed Tomography With Semiconductor Camera. Circ J 2016; 80: 689–95.

16. Berman DS, Abidov A, Kang X, et al. Prognostic validation of a 17-segment score derived from a 20-segment score for myocardial perfusion SPECT interpretation. J Nucl Cardiol 2004; 11: 414–23.

17. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. J Nucl Cardiol. 2002; 9: 240–5.

18. 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.

19. 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.

20. Zhang Y, Chan AK, Yu CM, et al. Left ventricular systolic asynchrony after acute myocardial infarction in patients with narrow QRS complexes. Am Heart J 2005; 149: 497–503.

21. Legallois D, Marie PY, Franken PR, et al. 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; doi: 10.1007/s12350-018-01546-2.

22. Sillanmäki S, Gimelli A, Ahmad S, et al. Mechanisms of left ventricular dyssynchrony: A multinational SPECT study of patients with bundle branch block. J Nucl Cardiol. 2020; doi: 10.1007/s12350-020-02054-y.

23. Japanese Circulation Society. The Japanese registry of all cardiac and vascular diseases Annual Report 2018. http://jroadinfo.ncvc.go.jp/

24. Tsutsui H, Isobe M, Ito H, et al on behalf of the Japanese Circulation Society and the Japanese Heart Failure Society Joint Working Group. JCS 2017/JHFS 2017 Guideline on Diagnosis and Treatment of Acute and Chronic Heart Failure - Digest Version. Circ J 2019; 83: 2084–184.

25. Tsuji K, Sakata Y, Nochioka K, et al. CHART-2 Investigators. Characterization of heart failure patients with mid-range left ventricular ejection fraction-a report from the CHART-2 Study. Eur J Heart Fail 2017; 19: 1258–69.

26. Kirtane AJ, Doshi D, Leon MB, et al. Treatment of higher-risk patients with an indication for revascularization: evolution within the field of contemporary percutaneous coronary intervention. Circulation 2016; 134: 422–31.

27. Ng AC, Tran da T, Allman C, et al. Prognostic implications of left ventricular dyssynchrony early after non-ST elevation myocardial infarction without congestive heart failure. Eur Heart J 2010; 31: 298–308

28. Chung ES, Leon AR, Tavazzi L, et al. Results of the Predictors of Response to CRT

(PROSPECT) trial. Circulation. 2008; 117: 2608–16.

29. Trimble MA, Velazquez EJ, Adams GL, et al. Repeatability and reproducibility of phase analysis of gated single-photon emission computed tomography myocardial perfusion imaging used to quantify cardiac dyssynchrony. Nucl Med Commun 2008; 29: 374–81

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.

Figure legends

Figure 1. A representative phase histogram and phase polar map in a patient with no LV mechanical dyssynchrony (A) and severe LV mechanical dyssynchrony (B). SD: standard deviation; LV: left ventricular.

Figure 2. ROC curves of the stress phase bandwidth for detection of MCEs. MCE: major cardiac event; ROC: receiver operating characteristic; AUC: area under the curve.

Figure 3. CAG, polar map of SPECT MPI, and phase analysis in representative cases. Each picture shows coronary angiographic images, polar map images, phase histograms, and phase map images from three representative patients with severe stenosis in the RCA proximal region (A), LAD and LCX proximal regions (B), or LCX proximal region (C). The polar map images, phase histograms, and phase map images on the top and bottom were obtained under stress and during rest, respectively. CAG: coronary angiography; LAD: left anterior descending artery; LCX: left circumflex artery; MPI: myocardial perfusion imaging; RCA: right coronary artery; SPECT: single-photon emission computed tomography.

Figure 4. Kaplan-Meier curves of the MCE-free survival in patients with a low (≤52°) or high (>52°) stress phase bandwidth. MCE: major cardiac event.

Figure 5. Kaplan-Meier curves of the MCE-free survival in patients with a low (≤52°) or high (>52°) stress phase bandwidth in the low (A) and high (B) ischemia groups. Low and high ischemia were SDS% ≤12.5% and SDS% >12.5%, respectively. MCE: major cardiac event;

SDS: summed difference score.

Table 1. Baseline characteristics of patients with low (≤52°) or high (>52°) stress phase bandwidth

	Stress phase bandwidth ≤ 52°		Stress phase bandwidth > 52°		P value
	n = 209		n = 106		
Male gender	169	81%	88	83%	0.6411
Age	68 ±	10	68 ±	11	0.8918
History of MI	51	24%	41	39%	0.0086
History of revascularization	72	34%	50	47%	0.0288
Hypertension	180	86%	100	94%	0.0286
Diabetes mellitus	79	38%	61	58%	0.0009
Hyperlipidemia	180	86%	95	90%	0.3790
Smoking	68	33%	43	41%	0.1593
Aspirin	203	97%	100	94%	0.2224
Thienopyridines	180	86%	86	81%	0.2488
Statins	171	82%	91	86%	0.7113
β-blockers	96	46%	67	63%	0.0038
Calcium channel blockers	126	60%	61	58%	0.6404
Nitrates	59	28%	26	25%	0.4851
ARB	107	51%	65	61%	0.0886
ACE Inhibitors	25	12%	17	16%	0.3154
Insulin users	10	5%	19	18%	0.0001
NT-proBNP (pg/mL)	130 (66 – 284)		790 (272 – 2979)		0.0006
eGFR (mL/min/1.73 m^2)	63.5 ±	21.9	52.7 ±	24.8	0.0001
QRS width (ms)	97.3 ±	15.6	107.3 ±	22.3	<0.0001

MI: myocardial infarction; ARB: angiotensin receptor blocker; ACE: angiotensin converting enzyme; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; eGFR: estimated glomerular filtration rate

Table 2. Comparison of visual % myocardium, cardiac functions, angiographic findings, and MCE rates in patients with low (≤52°) or high (>52°) stress phase bandwidth

	Stress phase bandwidth ≤ 52° n = 209		Stress phase bandwidth > 52° n = 106		P value
SSS%	15.8 ± 8.4		25.4 ± 12.2		<0.0001
SRS%	2.0 ± 3.6		9.6 ± 10.6		<0.0001
SDS%	13.8 ± 7.6		15.8 ± 8.9		0.0463
Rest LVEF (%)	69.7 ± 8.5		53.9 ± 13.0		<0.0001
Rest LVEDV (mL)	84.2 ± 28.7		137.5 ± 60.9		<0.0001
Rest LVESV (mL)	26.7 ± 15.6		68.7 ± 46.1		<0.0001
Stress LVEF (%)	63.2 ± 8.6		45.6 ± 11.1		<0.0001
Stress LVEDV (mL)	91.8 ± 28.8		152.2 ± 63.6		<0.0001
Stress LVESV (mL)	35.2 ± 18.3		87.7 ± 50.8		<0.0001
Rest phase SD (º)	13.1 ± 5.7		27.2 ± 13.7		<0.0001
Rest phase bandwidth (º)	47.3 ± 19.5		85.6 ± 35.5		<0.0001
Stress phase SD (º)	9.5 ± 3.0		25.3 ± 9.4		<0.0001
Stress phase bandwidth (º)	33.8 ± 10.0		82.5 ± 22.6		<0.0001
Perfusion defects in the region of LAD	116	56%	81	76%	0.0003
Perfusion defects in the region of RCA	103	49%	52	49%	0.9698
Perfusion defects in the region of LCX	63	30%	54	51%	0.0003
Angiographic CAD					
1-vessel CAD	82	39%	24	23%	0.0033
2-vessel CAD	79	38%	39	37%	0.8618
3-vessel CAD	48	23%	43	41%	0.0011
CTO vessels	55	26%	51	48%	0.0001
Revascularization					
PCI	192	92%	87	82%	0.0110
POBA	9	5%	2	2%	0.3431
BMS	12	6%	1	1%	0.0616
DES	171	89%	84	97%	0.0391
Multivessel PCI	47	22%	26	25%	0.6856
CABG	17	8%	19	18%	0.0110
Complete revascularization	182	87%	77	73%	0.0016
Repeat revascularization	16	8%	11	10%	0.4156
MCE rates	10	5%	25	24%	<0.0001

Cardiac death	0	0%	5	5%	0.0016
Non-fatal MI	1	1%	2	2%	0.2247
UAP	6	3%	5	5%	0.3998
Severe heart failure	3	1%	13	12%	<0.0001

MCE: major cardiac event; 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; SD: standard deviation; .LAD: Left anterior descending artery; RCA: right coronary artery; LCX: left circumflex artery; CAD: coronary artery disease; CTO: chronic total occlusion; PCI: percutaneous coronary intervention; POBA: percutaneous old balloon angioplasty; BMS: bare-metal stent; DES: drug-eluting stent; CABG: coronary artery bypass grafting; MI: myocardial infarction; UAP: unstable angina pectoris.

Table 3. Univariate and multivariate predictors for the high (>52°) stress phase bandwidth

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	*P* value
Age	1.0016	0.9788 – 1.0250	0.8914			
Male patients	1.1571	0.6268 – 2.1362	0.6408			
History of MI	1.9541	1.1824 – 3.2297	0.0090			
History of revascularization	1.6989	0.8830 – 2.7353	0.0292			
Hypertension	1.8651	1.8034 – 3.9396	0.1023			
Diabetes mellitus	2.2307	1.3859 – 3.5903	0.0010			
NT-proBNP	1.0000	1.0000 – 1.0001	0.0059			
eGFR	0.9805	0.9706 – 0.9906	0.0002			
SSS%	1.0937	1.0652 – 1.1230	<0.0001			
SRS%	1.2041	1.1404 – 1.2713	<0.0001	1.0911	1.0279 – 1.1582	0.0042
SDS%	1.0290	1.0002 – 1.0586	0.0484			
Rest LVEF	0.8721	0.8448 – 0.9002	<0.0001			
Rest LVEDV	1.0347	1.0256 – 1.0439	<0.0001			
Rest LVESV	1.0648	1.0481 – 1.0818	<0.0001			
Stress LVEF	0.8401	0.8084 – 0.8731	<0.0001	0.8574	0.8234 – 0.8928	<0.0001
Stress LVEDV	1.0370	1.0278 – 1.0463	<0.0001			
Stress LVESV	1.0608	1.0460 – 1.0758	<0.0001			
Perfusion defects in the region of LAD	2.5976	1.5368 – 4.3907	0.0004			
Perfusion defects in the region of RCA	0.9910	0.6209 – 1.5817	0.9698			
Perfusion defects in the region of LCX	2.4066	1.4862 – 3.8970	0.0004	2.4753	1.2614 – 4.8573	0.0084
3-vessel CAD	2.2894	1.3828 – 3.7904	0.0013			
CTO vessels	2.5964	1.5908 – 4.2375	0.0001			

CI: confidence interval; MI: myocardial infarction; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; eGFR: estimated glomerular filtration rate; 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; LAD: Left anterior descending artery; RCA: right coronary artery; LCX: left circumflex artery; CAD: coronary artery disease; CTO: chronic total occlusion.

Table 4. Background characteristics of patients with and without MCEs

	MCEs (+)		MCEs (−)		P value
	n = 35		n = 280		
Male patients	29	83%	228	81%	0.8374
Age	69 ±	11	68 ±	10	0.4345
History of MI	16	46%	76	27%	0.0229
History of revascularization	22	63%	100	36%	0.0019
Hypertension	33	94%	247	88%	0.2820
Diabetes mellitus	20	57%	120	43%	0.1094
Hyperlipidemia	31	89%	244	87%	0.8112
Smoking	12	34%	99	35%	0.9006
β-blockers	26	74%	137	49%	0.0047
ARB	21	60%	151	54%	0.4971
ACE Inhibitors	8	23%	34	12%	0.0792
NT-proBNP (pg/mL)	2591 (561 − 15150)		179 (80 − 575)		<0.0001
eGFR (mL/min/1.73 m^2)	44.5 ± 29.5		61.8 ± 21.9		<0.0001
SSS%	22.6 ± 14.3		18.6 ± 10.3		0.0405
SRS%	9.8 ± 13.0		3.9 ± 6.5		<0.0001
SDS%	12.8 ± 6.9		14.7 ± 8.2		0.1979
Rest LVEF(%)	55.1 ± 16.9		65.5 ± 11.6		<0.0001
Rest LVEDV (mL)	137.8 ± 62.2		97.7 ± 45.5		<0.0001
Rest LVESV (mL)	69.8 ± 50.4		37.2 ± 31.6		<0.0001
Stress LVEF(%)	47.3 ± 13.4		58.5 ± 12.0		<0.0001
Stress LVEDV (mL)	152.7 ± 64.9		107.1 ± 48.1		<0.0001
Stress LVESV (mL)	87.0 ± 53.8		48.6 ± 37.4		<0.0001
Rest phase SD (º)	24.8 ± 14.5		17.0 ± 10.6		0.0001
Rest phase bandwidth (º)	77.8 ± 41.2		58.0 ± 29.6		0.0004
Stress phase SD (º)	22.9 ± 12.3		13.8 ± 8.7		<0.0001
Stress phase bandwidth (º)	74.6 ± 35.9		47.1 ± 25.0		<0.0001
Perfusion defects in the region of LAD	28	80%	169	60%	0.0238
Perfusion defects in the region of RCA	17	49%	138	49%	0.9366
Perfusion defects in the region of LCX	16	46%	101	36%	0.2664
3-vessel CAD	13	37%	78	28%	0.2539
CTO vessels	13	37%	93	33%	0.6434

MCE: major cardiac event; MI: myocardial infarction; ARB: angiotensin receptor blocker; ACE: angiotensin converting enzyme; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; eGFR: estimated glomerular filtration rate: 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; SD: standard deviation; .LAD: Left anterior descending artery; RCA: right coronary artery; LCX: left circumflex artery; CAD: coronary artery disease; CTO: chronic total occlusion.

Table 5. Univariate and multivariate predictors for MCEs

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Age	1.0167	0.9828 – 1.0518	0.3372			
Male gender	1.1348	0.4711 – 2.7338	0.7779			
History of MI	2.3214	1.1921 – 4.5203	0.0133			
History of revascularization	3.0136	1.5170 – 5.9865	0.0016			
Hypertension	1.8030	0.5522 – 5.8873	0.3289			
Diabetes mellitus	1.7525	0.8970 – 3.4239	0.1006			
NT-proBNP	1.0000	1.0000 – 1.0000	<0.0001			
eGFR	0.9729	0.9611 – 0.9848	<0.0001	0.9773	0.9648 – 0.9900	0.0005
SSS%	1.0325	1.0043 – 1.0614	0.0235			
SRS%	1.0600	1.0315 – 1.0892	<0.0001			
SDS%	0.9745	0.9294 – 1.0218	0.2851			
Rest LVEF	0.9503	0.9291 – 0.9720	<0.0001			
Rest LVEDV	1.0084	1.0045 – 1.0124	<0.0001			
Rest LVESV	1.0118	1.0068 – 1.0169	<0.0001			
Stress LVEF	0.9463	0.9243 – 0.9689	<0.0001			
Stress LVEDV	1.0087	1.0050 – 1.0124	<0.0001			
Stress LVESV	1.0108	1.0063 – 1.0153	<0.0001			
Rest phase SD	1.0375	1.0170 – 1.0584	0.0003			
Rest phase bandwidth	1.0136	1.0057 – 1.0215	0.0007			
Stress phase SD	1.0556	1.0327 – 1.0790	<0.0001			
Stress phase bandwidth	1.0221	1.0138 – 1.0305	<0.0001	1.0195	1.0107 – 1.0284	<0.0001
Perfusion defects in the region of LAD	2.6212	1.1441 – 6.0051	0.0227			
Perfusion defects in the region of RCA	0.9524	0.4908 – 1.8483	0.8853			
Perfusion defects in the region of LCX	1.5262	0.7844 – 2.9694	0.2131			
3-vessel CAD	1.4688	0.7398 – 2.9159	0.2719			
CTO vessels	1.1114	0.5597 – 2.2071	0.7628			

CI: confidence interval; MI: myocardial infarction; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; eGFR: estimated glomerular filtration rate; 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; SD: standard deviation; LAD: Left anterior descending artery; RCA: right coronary artery; LCX: left circumflex artery; CAD: coronary artery disease; CTO: chronic total occlusion.
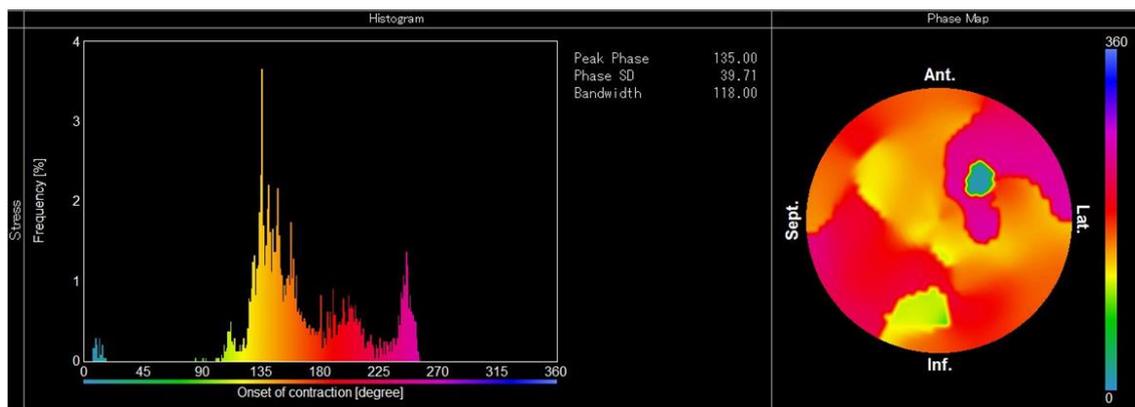
Figure 1

(A)

Phase SD 3.94   Phase bandwidth 14.00

(B)

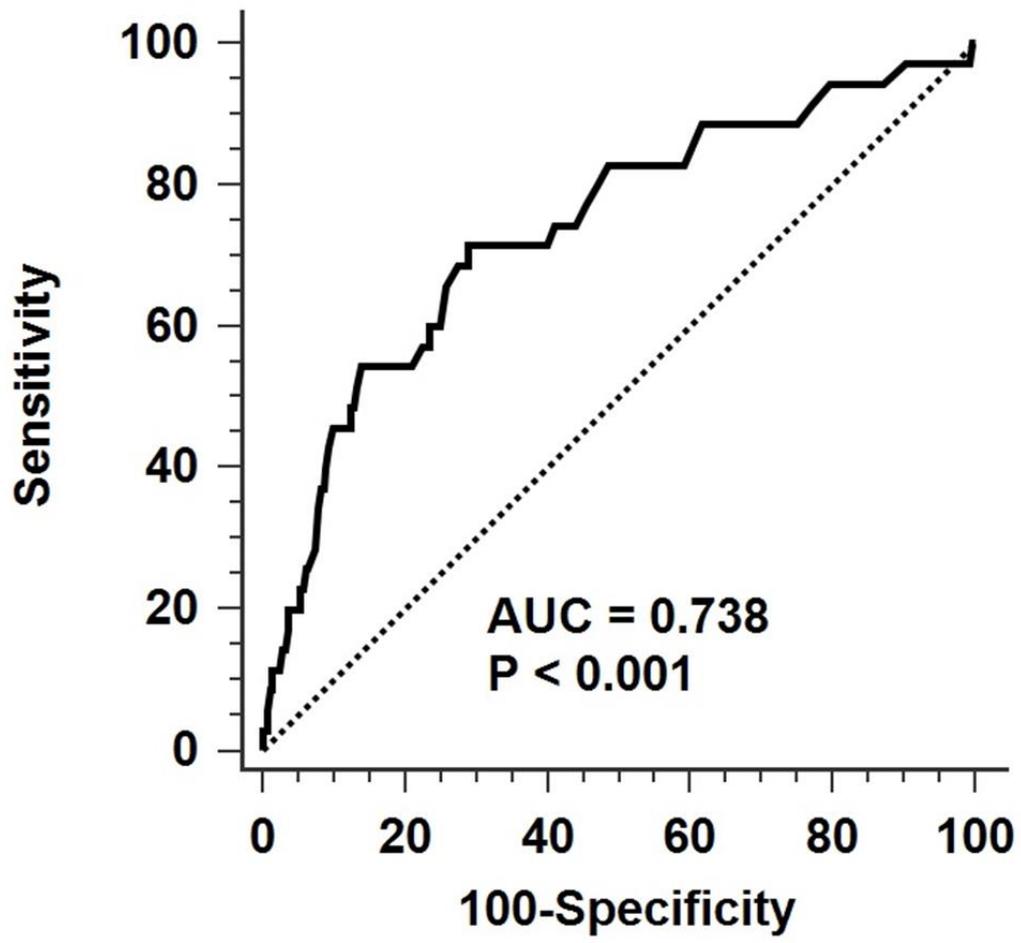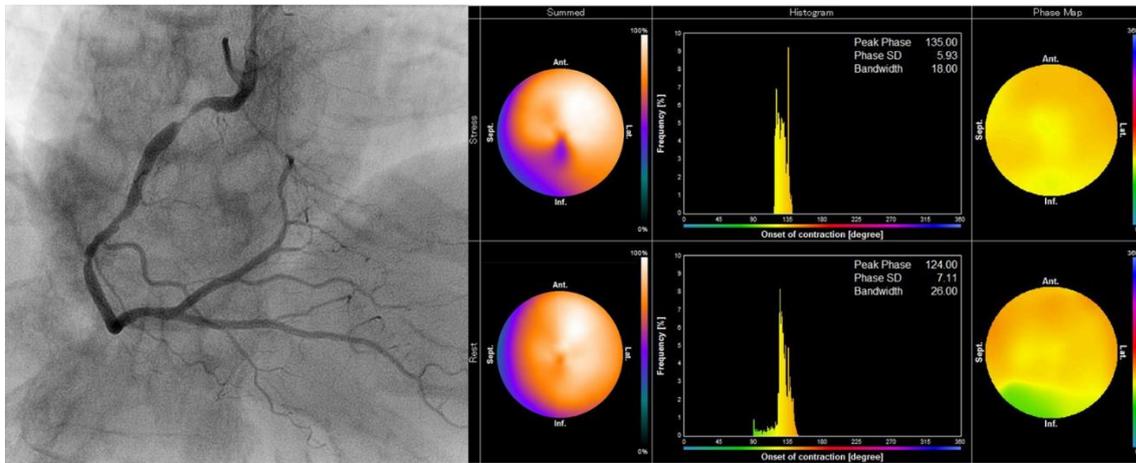
Phase SD 39.71   Phase bandwidth 118.00

Figure 2
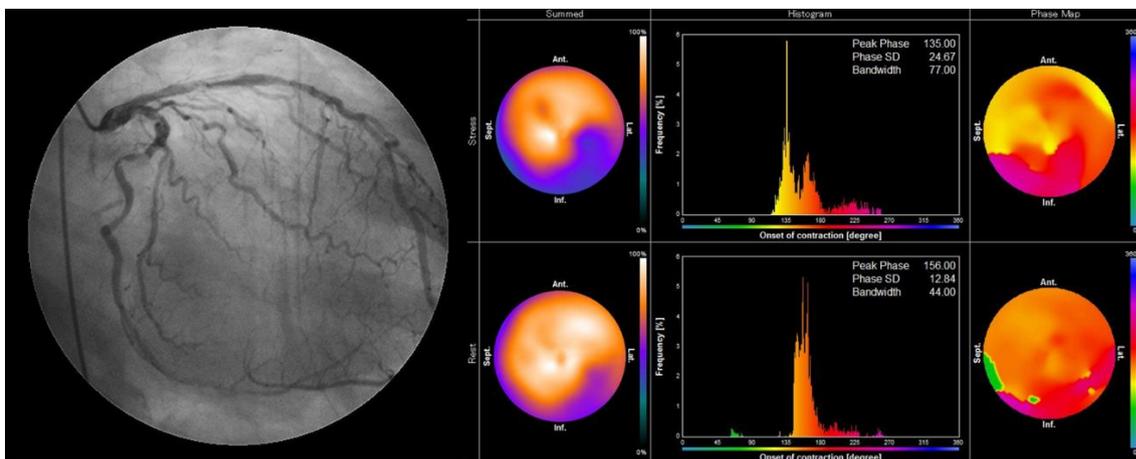
Figure 3

(A)

(B)

(C)

Figure 4

Figure 5

(A)

(B)