

## ORIGINAL ARTICLE

# Diagnostic Value of Vasodilator-Induced Left Ventricular Dyssynchrony as Assessed by Phase Analysis to Detect Multivessel Coronary Artery Disease

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## Abstract

**Purpose:** Phase analysis was recently developed to allow left ventricular (LV) mechanical dyssynchrony to be assessed by gated single-photon emission computed tomography (SPECT). However, few studies have analyzed LV dyssynchrony during pharmacological stress and at rest by applying phase analysis to detect multivessel coronary artery disease (CAD) using the SyncTool™.

**Methods:** Adenosine triphosphate (ATP) loading electrocardiogram-gated <sup>99m</sup>Tc-sestamibi SPECT was performed on 180 patients with suspected or known CAD. LV dyssynchrony was evaluated using the SyncTool™; the phase standard deviation (SD) and histogram bandwidth were derived.

**Results:** The summed stress score (SSS), summed difference score (SDS), post-stress increase in phase SD, and histogram bandwidth were greater in 78 patients with multivessel CAD than in 102 patients with insignificant or single-vessel CAD. In the detection of multivessel CAD, SSS of >9 and SDS of >5 showed sensitivities of 74% and 74%, and specificities of 71% and 78% respectively, whereas an increase in phase SD >8.3° and in histogram bandwidth >16° after ATP loading had sensitivities of 62% and 74% and specificities of 77% and 68%, respectively. A multivariate logistic analysis revealed that the identification of multivessel CAD was superior with the combination of a post-ATP increase in phase SD, increase in histogram bandwidth, and SDS (sensitivity 82%, specificity 76%, chi-square = 80.0) than with SDS alone (sensitivity 74%, specificity 78%, chi-square = 58.9).

**Conclusion:** The addition of ATP-induced LV dyssynchrony parameters to conventional perfusion analysis enabled the superior identification of patients with multivessel CAD.

**Keywords:** Coronary artery disease, Quantitative gated single-photon emission computed tomography, Phase analysis, Left ventricular dyssynchrony

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The development of electrocardiogram-gated single-photon emission computed tomography (SPECT) has facilitated the assessment of left ventricular (LV) function not only at rest, but also after stress which has, in turn, enabled the superior detection of coronary artery disease (CAD), particularly that involving multivessel pathology (1-4). A novel technique was

recently developed to evaluate LV mechanical dyssynchrony using phase analysis of gated SPECT (5,6). Previous studies applied this method and reported the diagnostic and prognostic values of LV mechanical dyssynchrony in patients with heart failure (7-9). Other studies attempted to analyze LV mechanical dyssynchrony after stress and at rest in order to detect

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a particular subset of CAD, and achieved this by applying count-based temporal and spatial phase analyses (10,11) because LV regional disparities in contractility are known to occur during periods of demand ischemia, such as during exercise or the infusion of dobutamine (12,13). Although the use of a pharmacological agent such as adenosine or dipyridamole has become the predominant method for inducing stress during myocardial SPECT in the current aging population (14,15), to the best of our knowledge, the SyncTool™ has not yet been employed to assess the indices of vasodilator-induced LV mechanical dyssynchrony. Considering the diagnostic challenge of multivessel CAD due to balanced ischemia using myocardial SPECT (16-20), we retrospectively determined whether vasodilator-induced LV mechanical dyssynchrony as assessed by phase analysis had an incremental diagnostic value in the detection of multivessel CAD over conventional perfusion analysis.

## Methods

### Study patients

Subjects comprised 180 consecutive patients (118 men and 62 women; mean age  $69 \pm 9$  years) with suspected or known CAD (based on clinical symptoms, coronary risk profiles, electrocardiographic findings, or a past medical history) who also underwent coronary angiography within 3 months of myocardial perfusion imaging between January 2003 and May 2010. Myocardial infarction had previously occurred in 40 patients. Patients with acute myocardial infarction or unstable angina within 1 month before the study, and those with atrial fibrillation, a left bundle branch block, ventricular pacing, or cardiomyopathy were excluded. Written informed consent for invasive coronary angiography was obtained from all participants. This retrospective study was approved by the Ethics Committee of Tokyo Medical University (No. 1470).

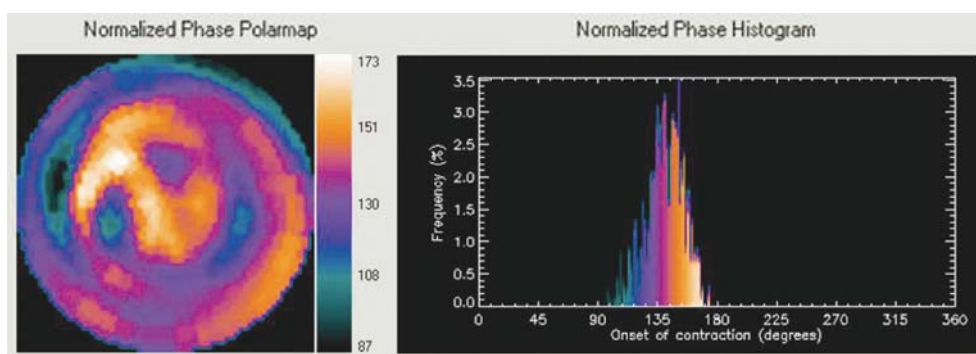
### Stress myocardial perfusion imaging

Stress myocardial perfusion imaging was performed using the 1-day protocol. Patients were requested not to consume caffeine for 12 hours before the test. Adenosine triphosphate (ATP) ( $0.16 \text{ mg/kg/min}$ ) was administered intravenously for 6 minutes (21). Three minutes after the administration of ATP,  $^{99\text{m}}\text{Tc}$ -sestamibi (259 MBq) was given intravenously. Imaging was started 30 minutes after the ATP administration. After 4 hours, the patients were given  $^{99\text{m}}\text{Tc}$ -sestamibi (777 MBq) while at rest. Electrocardiogram-gated myocardial SPECT was performed 30 minutes later.

Data were acquired with a 3-detector gamma camera (Prism 3000XP, Picker, Cleveland, OH) in 360-degree arcs (in 6-degree-wide directions, taking 30 seconds per projection, 20 times). A low-energy high-resolution parallel multihole collimator was used. The maximum matrix size was  $64 \times 64$ . When obtaining electrocardiogram-gated images, the R-R interval was divided by the R wave trigger into 8 equal portions. End-diastolic and end-systolic myocardial perfusion images were obtained with this method. All patients were in sinus rhythm during image acquisition. SPECT images were reconstructed from the data with a data processor (Odyssey VP, Picker) combined with a Butterworth filter (order 8; cutoff frequency 0.25 cycles/pixel) and ramp filter.

In accordance with a previous method, each SPECT image was divided into 20 segments (22). Radiopharmaceutical accumulation in the myocardium was visually evaluated by 2 cardiologists (blinded to clinical data) using a 5-grade scale: 0 (normal), 1 (slight reduction in uptake), 2 (moderate reduction in uptake), 3 (severe reduction in uptake), or 4 (absence of radioactive uptake). The total scores for all segments during exercise and at rest were designated as the summed stress scores (SSS) and summed rest scores (SRS), respectively. SSS minus SRS was defined as the summed difference score (SDS). Disagreements in image interpretation were resolved by consensus after extensive discussion among 2 of the 3 experts (S.H., H. T., or T.C.). In addition, the transient ischemic dilation (TID) ratio (i.e., the ratio of LV volumes at stress and at rest) was derived using the QPS program (Cedars-Sinai, Los Angeles, CA) (23).

Each reconstructed short-axis electrocardiogram-gated SPECT image was processed, and LV functional parameters (LV end-diastolic volume, LV end-systolic volume, and LV ejection fraction) were automatically obtained as described by Germano et al. (24). Gender-specific normal limits for LV volumetric measurements were derived from the Japanese Assessment of Cardiac Events and Survival Study by the Quantitative Gated SPECT (J-ACCESS) database: 130 ml for the LV end-diastolic volume and 60 ml for LV end-systolic volume in men, and 90 ml for LV end-diastolic volume and 40 ml for the LV end-systolic volume in women (25). In addition, a 3-dimensional count distribution was extracted from each of the LV short-axis datasets and subjected to a Fourier analysis. This generated a phase distribution ( $0$  to  $360^\circ$ ) spanning the entire R-R interval, which was displayed on a polar map and histogram (Fig. 1). Two indices related to LV dyssynchrony were automatically extracted using the



**Fig. 1** Representative phase polar map and phase histogram. A three-dimensional count distribution was extracted from each of the LV short-axis datasets and subjected to a Fourier analysis, which generated a phase distribution (0 to 360°) spanning the entire R-R interval.

SyncTool™ in conjunction with the Emory Cardiac Toolbox (Emory University/Syntermed Inc., Atlanta, GA) (5). Manual base parameter placement was used to define the margin of the cardiac base, but only if low-frequency noise located at the basal end of the ventricles was observed (26). The indices used were histogram bandwidth, which marked the range of degrees of the cardiac cycle during which 95% of the myocardium initiated contraction, and phase standard deviation (SD), which represented the SD of the phase distribution (Fig. 1). Furthermore, changes in phase SD and histogram bandwidth with stress were calculated as follows: phase SD after stress minus phase SD at rest or histogram bandwidth after stress minus histogram bandwidth at rest (10).

### Coronary angiography

Multidirectional coronary angiography was performed within 3 months of the scintigraphic study in all patients using Judkins' method. The degree of coronary artery stenosis was visually rated according to the criteria of the American Heart Association (27). Significant stenosis was considered to be present when  $\geq 75\%$  narrowing of the diameter was observed. Multivessel CAD was defined as 2- or 3-vessel CAD, or 1-vessel CAD involving significant stenosis in the left main trunk.

### Statistical analysis

Results were expressed as the mean  $\pm$  SD. The Student *t*-test was used to compare the means of continuous variables, and contingency tables were analyzed using the chi-square test. Receiver-operating characteristic (ROC) curves were analyzed to determine the optimal cut-off values of the SSS, SRS, SDS, TID ratio, changes in phase SD with stress, and histogram bandwidth with stress to predict multivessel

CAD. Sensitivity and specificity were calculated for these cut-off points using standard formulas. A univariate analysis was conducted with the logistic regression method, and a stepwise multivariate analysis was performed with the multiple logistic regression method using significant variables identified by the univariate analysis. We performed a linear discriminant analysis with stepwise variable selection with Wilks' lambda, which is the ratio of the within-groups sum of squares to the total sum of squares, in order to assess the potential to correctly identify multivessel CAD, using independent variables in the multivariate analysis. Bayes rule with equal prior probability was used for identification, and results were presented as sensitivity, specificity, and accuracy. A *p*-value of  $<0.05$  was considered to indicate a significant difference. Statistical computations were performed using SPSS 11.0 (SPSS Inc., Chicago, IL) and MedCalc 11.4 (MedCalc Software, Mariakerke, Belgium).

## Results

### Clinical characteristics and conventional perfusion analysis

All patients underwent coronary angiography; 1-vessel CAD was identified in 64 patients, 2-vessel CAD in 31, 3-vessel CAD in 47, and insignificant lesions in the remaining 38. Among the conventional scintigraphic parameters examined, the medians for SSS, SRS and SDS were 9, 3 and 5, respectively. No significant differences were observed in the prevalence of coronary risk factors, symptoms, or medications before the SPECT study, except for a higher prevalence of male gender and diabetes mellitus in patients with multivessel CAD than in those without (Table 1). SSS ( $13.9 \pm 6.6$  vs.  $7.6 \pm 5.5$ ;  $p < 0.0001$ ), SRS ( $5.6 \pm 4.9$  vs.  $3.6 \pm 4.0$ ;  $p < 0.01$ ), SDS ( $8.3 \pm 4.2$  vs.  $4.0 \pm 3.2$ ;  $p < 0.0001$ ), and the TID ratio ( $1.13 \pm 0.11$  vs.  $1.09 \pm 0.12$ ;

**Table 1** Clinical characteristics of 180 patients

	Multivessel CAD (+) (n = 78)	Multivessel CAD (-) (n = 102)	p-value
Age (years)	68 ± 10	70 ± 9	0.14
Men	60 (77%)	58 (57%)	<0.01
Height (cm)	162 ± 9	160 ± 9	0.32
Body weight (kg)	63 ± 10	61 ± 11	0.21
Body mass index	24.5 ± 2.9	24.3 ± 2.6	0.36
<b>Coronary risk factors</b>			
Hypertension	63 (81%)	78 (76%)	0.49
Dyslipidemia	47 (60%)	68 (67%)	0.38
Diabetes mellitus	44 (56%)	36 (35%)	<0.01
Smoking	41 (53%)	52 (51%)	0.99
Prior MI	18 (23%)	22 (22%)	0.81
Prior PCI	24 (31%)	35 (34%)	0.62
Prior CABG	2 (3%)	4 (4%)	0.62
<b>Medications</b>			
Aspirin	54 (69%)	71 (70%)	0.96
Beta-blocker	28 (36%)	35 (34%)	0.83
Calcium channel blocker	37 (47%)	59 (58%)	0.17
Nitrates	29 (37%)	27 (26%)	0.07
Statin	37 (47%)	52 (51%)	0.64

CAD=coronary artery disease, CABG=coronary artery bypass grafting, MI=myocardial infarction, PCI=percutaneous coronary intervention

$p < 0.05$ ) were significantly greater in the 78 patients with multivessel CAD than in the 102 patients with 1-vessel CAD or an insignificant lesion (Table 2).

### LV functional analysis

LV end-diastolic volume at rest ( $85.8 \pm 33.8$  vs.  $71.6 \pm 27.7$  ml;  $p < 0.01$ ) and end-systolic volume at rest ( $30.6 \pm 23.0$  vs.  $21.7 \pm 18.1$  ml;  $p < 0.01$ ) were significantly larger, whereas ejection fraction at rest ( $67.5 \pm 12.6$  vs.  $72.9 \pm 11.0\%$ ;  $p < 0.01$ ) was significantly lower in patients with multivessel CAD than in patients with 1-vessel CAD or an insignificant lesion (Table 2).

### Phase analysis

In all of the 180 patients, the means of phase SD at rest and after ATP loading were  $15.0^\circ \pm 8.9^\circ$  and  $22.2^\circ \pm 12.6^\circ$ , respectively, while the means of histogram bandwidth at rest and after ATP loading were  $44.1^\circ \pm 27.0^\circ$  and  $64.9^\circ \pm 39.0^\circ$ , respectively. The means of phase SD at rest and after ATP loading were  $14.1^\circ \pm 8.0^\circ$  and  $17.1^\circ \pm 10.4^\circ$ , respectively, in 32 patients with insignificant lesions who also did not have previous myocardial infarction. The means of histogram bandwidth at rest and after ATP loading were  $41.4^\circ \pm 24.4^\circ$  and  $52.5^\circ \pm 34.1^\circ$ , respectively.

Phase SD after ATP loading ( $27.1^\circ \pm 13.6^\circ$  vs.  $18.5^\circ \pm 10.5^\circ$ ;  $p < 0.0001$ ), histogram bandwidth after ATP

loading ( $79.1^\circ \pm 43.7^\circ$  vs.  $54.1^\circ \pm 31.0^\circ$ ;  $p < 0.0001$ ), and phase SD at rest ( $16.7^\circ \pm 10.2^\circ$  vs.  $13.7^\circ \pm 7.6^\circ$ ;  $p < 0.05$ ) were significantly larger in patients with multivessel CAD than in patients with 1-vessel CAD or an insignificant lesion, whereas no significant differences were observed in histogram bandwidth at rest ( $48.2^\circ \pm 29.0^\circ$  vs.  $40.9^\circ \pm 25.1^\circ$ ;  $p = 0.07$ ) (Table 2).

The distribution of the post-ATP increase in phase SD and increase in histogram bandwidth in patients with an insignificant lesion, 1-vessel CAD, and multivessel CAD is shown in Fig. 2. The increase in phase SD after ATP loading ( $10.5^\circ \pm 8.4^\circ$  vs.  $4.8^\circ \pm 8.9^\circ$ ;  $p < 0.0001$ ) and increase in histogram bandwidth after ATP loading ( $30.8^\circ \pm 26.1^\circ$  vs.  $13.2^\circ \pm 24.4^\circ$ ;  $p < 0.0001$ ) were significantly larger in patients with multivessel CAD than in patients with 1-vessel CAD or an insignificant lesion (Table 2, Fig. 2).

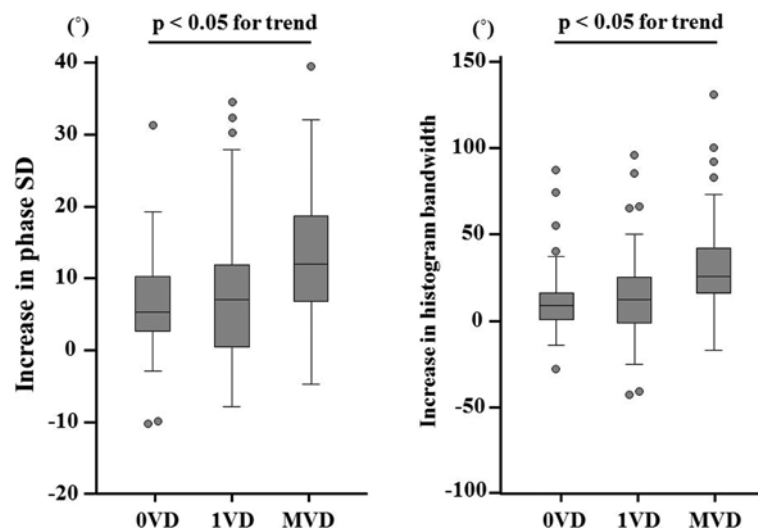
### Univariate analysis for the detection of multivessel CAD

We applied an ROC curve analysis to this group of patients in order to detect multivessel CAD with a myocardial perfusion analysis. The cut-off points for severe CAD were  $>9$  for SSS,  $>2$  for SRS,  $>5$  for SDS, and  $>1.04$  for the TID ratio (Fig. 3A). The respective sensitivities, specificities, and accuracies in the detection of multivessel CAD were 74%, 71%, and 72% with SSS,

**Table 2** Scintigraphic findings in patients with and without multivessel CAD

	Multivessel CAD (+) (n = 78)	Multivessel CAD (-) (n = 102)	p-value
<b>Myocardial perfusion</b>			
Summed stress score	13.9 ± 6.6	7.6 ± 5.5	<0.0001
Summed rest score	5.6 ± 4.9	3.6 ± 4.0	<0.01
Summed difference score	8.3 ± 4.2	4.0 ± 3.2	<0.0001
TID ratio	1.13 ± 0.11	1.09 ± 0.12	<0.05
<b>LV function at rest</b>			
End-diastolic volume (ml)	85.8 ± 33.8	71.6 ± 27.7	<0.01
End-systolic volume (ml)	30.6 ± 23.0	21.7 ± 18.1	<0.01
Ejection fraction (%)	67.5 ± 12.6	72.9 ± 11.0	<0.01
<b>LV phase analysis at rest</b>			
Phase SD	16.7 ± 10.2°	13.7 ± 7.6°	<0.05
Histogram bandwidth	48.2 ± 29.0°	40.9 ± 25.1°	0.07
<b>LV phase analysis after stress</b>			
Phase SD	27.1 ± 13.6°	18.5 ± 10.5°	<0.0001
Histogram bandwidth	79.1 ± 43.7°	54.1 ± 31.0°	<0.0001
<b>Change in LV phase analysis with stress</b>			
Phase SD	10.5 ± 8.4°	4.8 ± 8.9°	<0.0001
Histogram bandwidth	30.8 ± 26.1°	13.2 ± 24.4°	<0.0001

CAD = coronary artery disease, LV = left ventricular, SD = standard deviation, TID = transient ischemic dilation



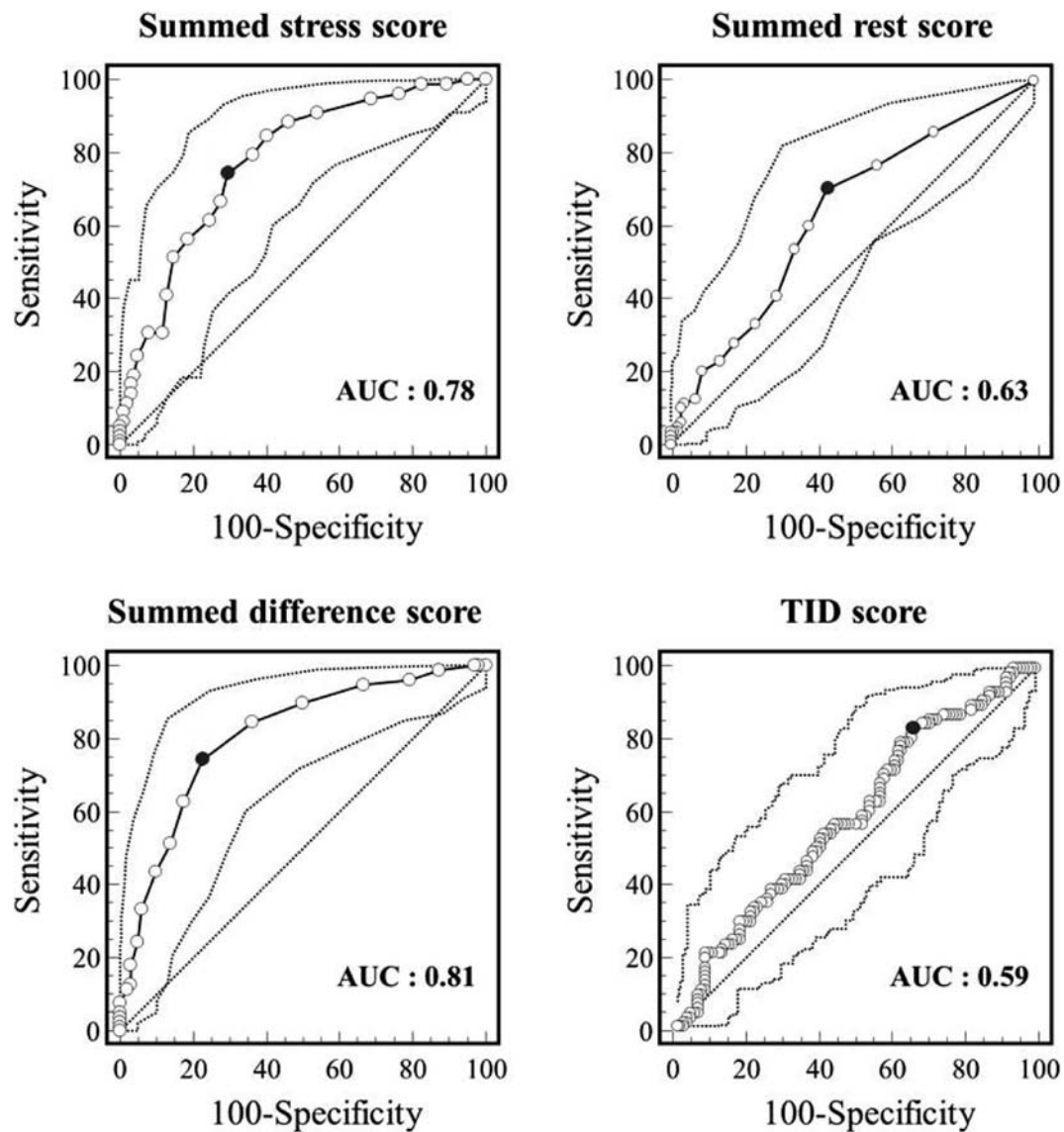
**Fig. 2** Distribution of the increase in phase SD and increase in histogram bandwidth in patients with an insignificant lesion, 1-vessel CAD, and multivessel CAD. Results are expressed as box-and-whisker plots; the central box covers the interquartile range, with the median indicated by the line within the box. The whiskers extend to the most extreme values within the 1.5 interquartile ranges. More extreme values are plotted individually. SD = standard deviation, CAD = coronary artery disease, 0VD = insignificant lesion, 1VD = 1-vessel disease, MVD = multivessel disease

74%, 78%, and 76% with SDS, and 83%, 34%, and 56% with the TID ratio, respectively (Table 3). An ROC curve analysis demonstrated that changes in the indices of LV dyssynchrony indicated multivessel CAD if a >8.3° increase in phase SD and a >16° increase in histogram bandwidth were observed after exercise (Fig. 3B). The sensitivities, specificities, and accuracies

in detecting multivessel CAD were 62%, 77%, and 70% with changes in phase SD, and 74%, 68%, and 71% with changes in histogram bandwidth, respectively (Table 3).

Sixteen out of 180 patients had normal myocardial perfusion images. Five out of these 16 patients had abnormal values for LV dyssynchrony. Among the 5



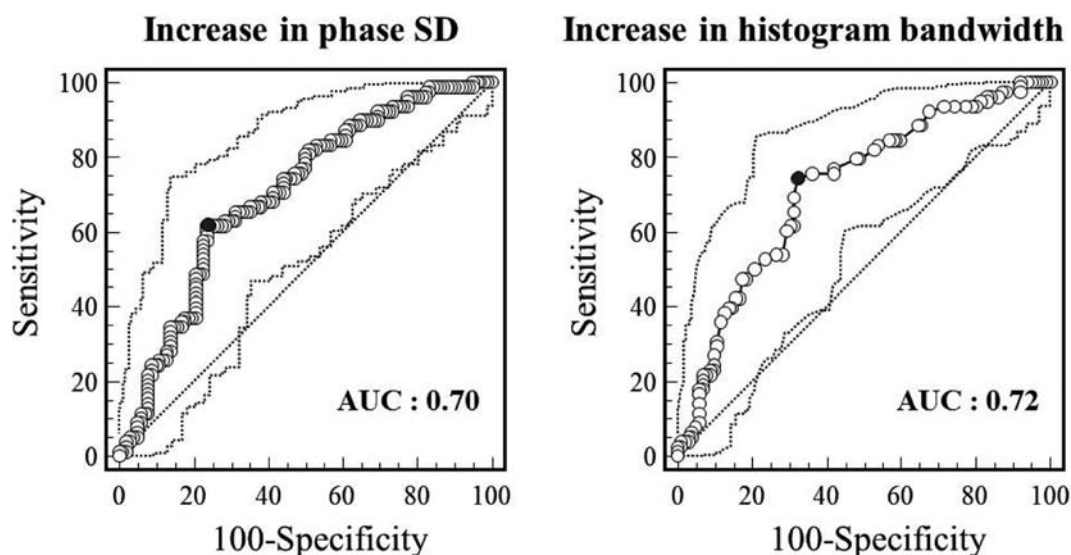


**Fig. 3A** Cut-off points for perfusion parameters and the TID ratio to detect multivessel CAD. Cut-off points for multivessel CAD were defined as a summed stress score of  $>9$ , summed rest score of  $>2$ , summed difference score of  $>5$ , and TID ratio of  $>1.04$ . The area under the curve (AUC) was 0.78 for the summed stress score, 0.63 for the summed rest score, 0.81 for the summed difference score, and 0.59 for the TID ratio. TID = transient ischemic dilation, CAD = coronary artery disease

**Table 3** Diagnostic values of scintigraphy parameters for multivessel CAD

	Sensitivity (%)	Specificity (%)	Accuracy (%)
Summed stress score $>9$	74	71	72
Summed rest score $>2$	71	57	63
Summed difference score $>5$	74	78	76
TID ratio $>1.04$	83	34	56
Dilated end-diastolic volume	26	81	57
Dilated end-systolic volume	32	83	61
Decreased ejection fraction	22	89	60
Increase in phase SD $>8.3^\circ$	62	77	70
Increase in histogram bandwidth $>16^\circ$	74	68	71

Abbreviations as in Table 2



**Fig. 3B** Cut-off points for the increase in phase SD and increase in histogram bandwidth to detect multivessel CAD. Cut-off points for multivessel CAD were defined as an increase in phase SD  $>8.3^\circ$  and increase in histogram bandwidth  $>16^\circ$ . The AUC was 0.70 for the increase in phase SD and 0.72 for the histogram bandwidth. SD = standard deviation, CAD = coronary artery disease

**Table 4** Detection of multivessel CAD: Univariate and multivariate analyses

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.0 (0.95-1.01)	0.139		
Men	2.5 (1.3-4.9)	$<0.01$		
Hypertension	1.3 (0.6-2.7)	0.488		
Diabetes mellitus	2.4 (1.3-4.4)	$<0.01$		
Dyslipidemia	0.8 (0.4-1.4)	0.375		
Smoking	1.0 (0.6-1.8)	0.996		
Summed stress score $>9$	7.0 (3.4-13.5)	$<0.0001$		
Summed rest score $>2$	3.2 (1.7-5.9)	$<0.0001$		
Summed difference score $>5$	10.0 (5.0-19.8)	$<0.0001$	8.2 (3.9-17.1)	$<0.0001$
TID ratio $>1.04$	2.6 (1.3-5.4)	$<0.01$		
Dilated end-diastolic volume	1.5 (0.7-3.1)	0.259		
Dilated end-systolic volume	2.4 (1.2-4.8)	$<0.05$		
Decreased ejection fraction	2.3 (1.1-5.3)	$<0.05$		
Increase in phase SD $>8.3^\circ$	5.2 (2.7-9.9)	$<0.0001$	2.6 (1.0-6.4)	0.042
Increase in histogram bandwidth $>16^\circ$	6.1 (3.1-11.7)	$<0.0001$	2.6 (1.1-6.4)	0.040

OR = odds ratio, CI = confidence interval

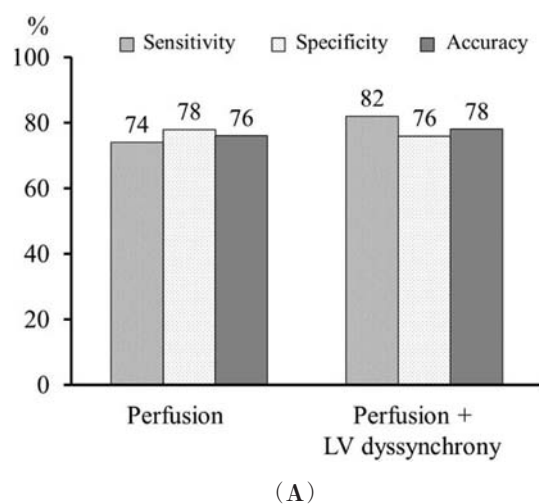
Other abbreviations as in Table 2

patients, 4 had significant CAD, revealing 3-vessel disease in 1, 2-vessel disease with RCA and LCx lesions in 1, 1-vessel disease with an LAD lesion in 1, and 1-vessel disease with an LCx lesion in 1, whereas the remaining patient had an insignificant lesion.

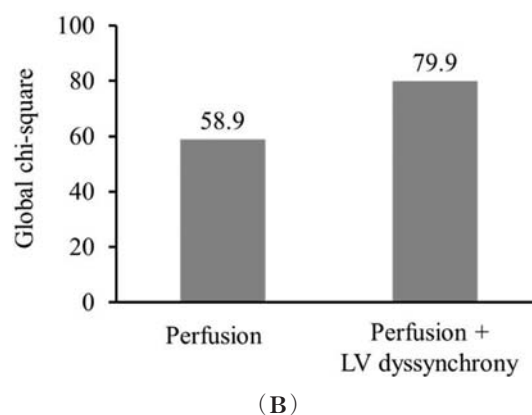
#### Multivariate analysis for the detection of multivessel CAD

To detect multivessel CAD, we performed a logistic regression analysis by entering 10 variables that were identified as significant by the univariate analysis (Table 4). The most important variable in the identifica-

tion of multivessel CAD was an SDS of  $>5$ , followed by an increase in histogram bandwidth of  $>16^\circ$  after ATP loading and an increase in the phase SD of  $>8.3^\circ$  after ATP loading (Table 4). A linear discriminant analysis using SDS yielded a sensitivity of 74%, specificity of 78%, and an accuracy of 76% (global chi-square = 58.9) (Figs. 4A, 4B). We repeated the discriminant analysis using SDS and mechanical dyssynchrony indices, which were identified as significant by the multivariate analysis. This analysis revealed that the identification of multivessel CAD was superior with the combination of a post-ATP increase in phase SD



**Fig. 4A** Comparison of diagnostic values with the addition of phase analysis in the detection of multivessel CAD. CAD = coronary artery disease



**Fig. 4B** Incremental diagnostic value with the addition of phase analysis to perfusion analysis in the detection of multivessel CAD. TID = transient ischemic dilation, CAD = coronary artery disease

increase in histogram bandwidth, and SDS (sensitivity 82%, specificity 76%, global chi-square = 79.9) than with SDS alone (Figs. 4A, 4B). A typical case is shown in Fig. 5.

## Discussion

We herein attempted to determine whether indices of ATP-induced LV mechanical dyssynchrony as assessed by phase analysis using the SyncTool™ had an incremental diagnostic value over conventional perfusion analysis for the detection of multivessel CAD. The results obtained demonstrated that the indices of LV mechanical dyssynchrony as assessed by a count-based phase analysis of ATP myocardial SPECT indicated an incremental diagnostic value over clinical and perfusion variables in the detection of multivessel disease, a high-risk subset of CAD. Compared with the indices of LV mechanical dyssynchrony at rest, a  $>8.3^\circ$  increase in phase SD or a  $>16^\circ$  increase in histogram bandwidth after ATP loading showed a sensitivity of 62% to 74% and specificity of 68% to 77% in the detection of multivessel CAD. A multivariate analysis revealed that that the identification of multivessel CAD was superior with the combination of a post-ATP increase in phase SD of  $>8.3^\circ$ , increase in histogram bandwidth of  $>16^\circ$ , and SDS of  $>5$  (sensitivity 82% and specificity 76%) than with SDS alone (sensitivity 74% and specificity 78%). The extensive and severe perfusion abnormalities represented by the summed scores are well-established scintigraphic markers for multivessel CAD (1,3). SDS of  $>5$  and SSS of  $>9$  correlated with multivessel CAD in this study. Furthermore, the addition of the indices of ATP-induced LV dyssynchrony to these standard

myocardial perfusion parameters significantly improved the diagnostic value (global chi-square, 79.9 vs. 58.9).

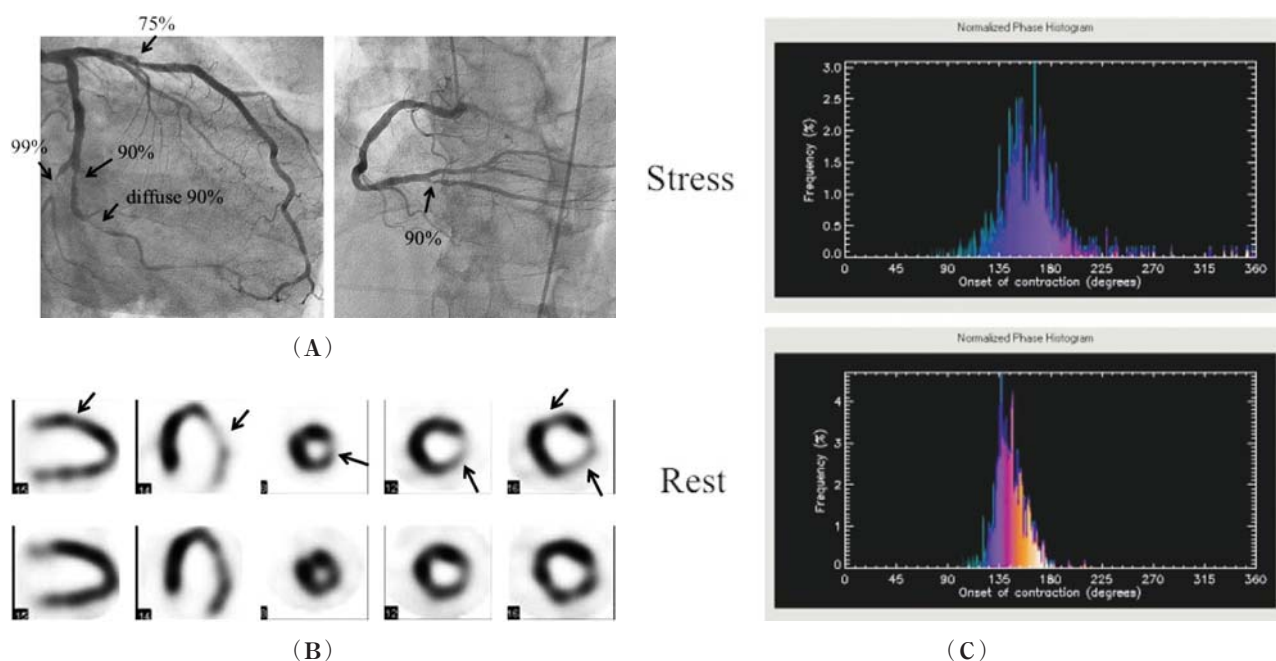
The diagnosis of multivessel CAD is considered important because a standard SPECT evaluation is known to often underestimate this high-risk subset due to balanced ischemia (16-20). To overcome this diagnostic challenge, numerous studies reported the usefulness of scintigraphic markers such as the diffuse slow washout, lung uptake of radiotracer and TID (16-20). In this regard, the application of the indices of LV dyssynchrony using phase analysis is considered a novel approach. The present study demonstrated the diagnostic importance of evaluating ATP-induced LV dyssynchrony indices using a phase analysis of gated SPECT in the identification of multivessel CAD.

## Comparison with previous studies

A limited number of studies have reported the diagnostic utility of phase analysis during stress and at rest using myocardial SPECT in CAD patients. Horigome et al. examined 18 CAD patients and 18 normal control subjects using regional LV temporal analysis at rest and after adenosine loading (11). They showed that the maximum difference in time to end-systole in the 17 segments (the most important index of mechanical dyssynchrony according to their method) increased after adenosine loading in CAD patients, but not in normal subjects. They concluded that a temporal delay in contraction may have been induced by adenosine in their study.

Using SyncTool™ for LV dyssynchrony, we previously evaluated 278 patients with suspected or known CAD by subjecting them to exercise stress, which imposes





**Fig. 5** Representative images of coronary angiogram and perfusion and phase analyses of a 75-year-old man. (A) Coronary angiography revealed 3-vessel CAD with intermediate stenosis of the left anterior descending coronary artery, and severe narrowing of the right coronary artery and left circumflex artery. (B) Reversible perfusion defects were observed in the anteroseptal and postero-lateral segments, with SSS, SRS, SDS, and a TID ratio of 14, 5, 9, and 1.09, respectively. (C) Phase distribution images (after stress [upper panel] and at rest [lower panel]) revealed that the increase in phase SD after exercise was  $20.2^\circ$  while that in histogram bandwidth was  $50^\circ$ . CAD = coronary artery disease, TID = transient ischemic dilation, SD = standard deviation

actual demand ischemia in patients with critical coronary artery stenosis (28). Our findings demonstrated that the indices of exercise-induced LV mechanical dyssynchrony as assessed by SyncTool™ on myocardial SPECT were the most important diagnostic parameters and had an incremental diagnostic value over clinical and perfusion variables in the detection of multivessel CAD.

The present study, combined with the aforementioned 2 studies, indicated that changes in the indices of LV mechanical dyssynchrony after exercise or pharmacological stress were related to stress-induced myocardial ischemia.

#### Possible mechanisms underlying ATP-induced changes in indices of LV mechanical dyssynchrony in patients with multivessel CAD

Two different mechanisms are considered responsible for generating cardiac dyssynchrony: temporal delays and contractile disparities (29). In contrast to patients with temporal delays due to a wide QRS, LV regional disparities in contractility are regarded as the predominant mechanism responsible for dyssynchrony in CAD patients (28,29). When activation occurs, one part of the LV wall, which has a normal myocardium under a

normal coronary artery, contracts more strongly than the other part of the LV wall with myocardial ischemia or fibrosis. The part considered as the strong wall pushes out the weaker wall, which contracts in early diastole (29-31). A delay in the contraction of the weak wall, imposed by exercise-induced ischemia or stunning, is thought to be depicted as the delayed onset of mechanical contraction by count-based temporal and spatial analyses of the phase using the SyncTool™. The exercise-induced increase in histogram bandwidth represented an area of the delayed initiation of myocardial contraction, while a greater phase SD accounted for a wide phase distribution in the current results. Thus, if the extent of ischemic myocardium was greater, the indices of LV mechanical dyssynchrony may also become elevated, particularly in patients with multivessel CAD (28).

Although ATP does not induce actual ischemia (in contrast to exercise stress), an increase in myocardial blood flow (induced by pharmacological vasodilation in a normal vascular territory) has been shown to result in greater myocardial contraction (21,32). Therefore, a difference may occur in contractility based on the amount of myocardial blood flowing during vasodilation in the presence or absence of coronary artery stenosis

(33,34). However, the impact of pharmacological vasodilation on the indices of LV mechanical dyssynchrony may be less than that of exercise stress, since the indices of mechanical dyssynchrony in exercise stress were found to be the most important in a previous study (28).

### Clinical implications

One of the major limitations of myocardial perfusion imaging is its spatial relativity in perfusion defect analysis (35). A high-risk group, such as those with left main and 3-vessel CAD, may be overlooked if physicians only rely on perfusion analysis (2,4,36). Lima et al. reported that the addition of a count-based wall thickening fraction with gated SPECT to conventional perfusion analysis improved sensitivity in detecting 3-vessel CAD without any loss in specificity (2). Phase analysis is also free of the limitations of relative perfusion defect analysis. The uniqueness of phase analysis is its temporal ability to focus on the timing of myocardial contraction in addition to its spatial distribution. Previous findings and the results of the present study underscore the diagnostic usefulness of phase analysis at rest and after stress in CAD patients with the application of exercise stress or pharmacological loading (28).

Phase analysis is a count-based method that measures mechanical dyssynchrony using the linear relationship between variations in regional maximum counts and myocardial wall thickening during a cardiac cycle, which may be affected by the count of the tracer. A previous study demonstrated that the reliable indices of phase analysis were observed by using gated SPECT data in common clinical settings, such as >10 counts per myocardial pixel (37), although the image count may be different in each image (after stress or at rest). In 38 patients with an insignificant lesion, the histogram bandwidth was significantly larger after ATP loading than at rest ( $54.4 \pm 36.0$  vs.  $40.8 \pm 23.1$ ;  $p=0.01$ ), whereas this difference was less than the cut-off value of  $>16^\circ$  for ATP-induced LV dyssynchrony. In contrast, no significant difference was observed in phase SD after ATP loading and at rest ( $17.9 \pm 11.2$  vs.  $14.0 \pm 7.7$ ;  $p=0.06$ ). Therefore, the count of the tracer had almost no effect on the indices of phase analysis if we used the current protocol developed by Chen, et al. (5).

In the present study, 16 patients had normal myocardial perfusion images. Of these patients, 5 had abnormal values for LV dyssynchrony. Among the 5 patients, 4 had significant CAD, revealing 3-vessel disease in 1, 2-vessel disease with RCA and LCx lesions in 1, 1-vessel disease with an LAD lesion in 1, and

1-vessel disease with an LCx lesion in 1, whereas the remaining 1 had an insignificant lesion. Since four-fifths of patients with normal myocardial perfusion images and abnormal values for LV dyssynchrony had significant CAD, LV dyssynchrony was considered to be due to actual myocardial ischemia, and not to the false positive findings of the LV dyssynchrony analyses.

### Study limitations

The present study was performed retrospectively, and, therefore, a prospective approach that applies stress myocardial SPECT with phase analysis and invasive coronary angiography to a large patient population is necessary.

The data of phase analysis were acquired at 8 frames per cardiac cycle in the present study. Higher temporal resolution may theoretically be obtained by acquisition at 16 frames per cardiac cycle. However, the current method was developed by Chen et al. in the recognition that the first-harmonic Fourier transformation enhanced phase analysis when applied to the data at 8 frames per cardiac cycle (38,39). Only the early systolic part of the cardiac cycle was used to determine the onset of mechanical contractions. Observations with a high degree of intra-observer and inter-observer reproducibility in the indices of LV mechanical dyssynchrony additionally demonstrated the feasibility of the method applied in the present study (26). Our previous study also showed excellent intra-observer reproducibility for phase SD ( $r=0.991$ ,  $p<0.0001$ ) and histogram bandwidth ( $r=0.998$ ,  $p<0.0001$ ), as well as inter-observer reproducibility for phase SD ( $r=0.997$ ,  $p<0.0001$ ) and histogram bandwidth ( $r=0.998$ ,  $p<0.0001$ ) (28).

### Conclusions

The present study demonstrated that the addition of count-based phase analysis to the evaluation of ATP-induced LV mechanical dyssynchrony by conventional SPECT perfusion analysis enabled the superior identification of patients with multivessel CAD.

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## Conflicts of Interest

We have no potential conflicts of interest to report for any of the activities.

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