

Relation of early post-stress left ventricular dyssynchrony and the extent of angiographic coronary artery disease

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Background. Previous studies showed different dyssynchrony patterns between ischemic and normal myocardium at early post-stress using TI-201 gated SPECT myocardial perfusion imaging (MPI). The aim of this study was to assess the relation of stress-induced dyssynchrony and the extent of angiographic coronary artery disease (CAD).

Methods and Results. The MPI images of 144 patients were retrospectively analyzed. With $\geq 70\%$ stenosis as the criteria of CAD, 57 had no CAD, 32 had 1-vessel disease, 36 had 2-vessel disease, and 19 had 3-vessel disease, respectively. LV global and territorial dyssynchrony parameters were measured by the phase analysis from stress/rest TI-201 SPECT MPI and compared between stress and rest among the patient groups. The patients with multi-vessel CAD had significantly more global dyssynchrony than the patients without $\geq 70\%$ stenosis at stress. The patients with multi-vessel CAD showed significantly more global and territorial dyssynchrony on stress images than on rest. More patients with 3-vessel CAD were correctly classified as multi-vessel disease, when combining both visual interpretation and dyssynchrony assessment.

Conclusion. The patients with multi-vessel CAD had significantly more global and territorial dyssynchrony at early post-stress than at rest. Such quantitative measures of myocardial stunning may assist in the diagnosis of multi-vessel CAD. (J Nucl Cardiol 2014;21:1048–56.)

Key Words: Thallium-201 • gated SPECT • left-ventricular dyssynchrony • myocardial ischemia

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INTRODUCTION

Myocardial stunning, defined as prolonged global and/or regional myocardial dysfunction after stress-induced ischemia, has been well described on stress/rest gated myocardial perfusion imaging (MPI).^{1,2} It might be manifested as transient post-stress decline of left-ventricular (LV) ejection fraction (EF) or reversible regional wall motion abnormality (RWA) on gated MPI and were found to correlate with the severity of stress-induced perfusion defects. Plenty of studies further demonstrated that stress-induced stunning shown on gated MPI correlated with severe and extensive coronary artery disease (CAD).^{3–6} It should be noted that the observation of myocardial stunning might be different when using different kinds of radiotracers (e.g., Tl-201, Tc-99m sestamibi, or Rb-82), imaging protocols (e.g., peak-stress, early post-stress, or post-stress), or different types of stress (e.g., exercise or pharmacological stress).

Phase analysis of gated MPI was first developed by Chen et al⁷ for measuring LV dyssynchrony. Previous studies have shown that quantitative indices given by phase analysis, such as phase standard deviation (SD) and phase histogram bandwidth, correlated well with LV dyssynchrony parameters measured by tissue Doppler echocardiography.^{8–10} These studies were done using Tc-99m labeled radiotracers (sestamibi or tetrofosmin) and usually acquired data 1 hour or more post injection. Therefore, the stress images represented the late post-stress function, close to the resting function. A study using Tc-99m sestamibi MPI reported that the presence of even large reversible defects did not alter LV dyssynchrony from rest to stress.¹¹

Chen et al first evaluated the performance of phase analysis of Tl-201 gated SPECT MPI in comparison with Tc-99m sestamibi and found a good correlation between the LV dyssynchrony parameters obtained from the images of these two tracers.¹² Furthermore, the same group investigated myocardial stunning in CAD patients using phase analysis of Tl-201 gated SPECT MPI and showed that stress-induced myocardial ischemia caused dyssynchronous contraction in the ischemic region, deteriorating LV synchrony.¹³ On the contrary, normal myocardium had more synchronous contraction at stress than at rest.¹³ The different dyssynchrony pattern between ischemic and normal myocardium at early post-stress may aid diagnosis of CAD using Tl-201 gated SPECT MPI.

This study followed the above studies in phase analysis of Tl-201 gated SPECT MPI in CAD patients. It was aimed to assess the relation of stress-induced LV dyssynchrony and the extent of angiographic CAD.

MATERIALS AND METHODS

Patients

The MPI images of 144 consecutive patients, who were referred for dipyridamole-stress/rest Tl-201 gated SPECT MPI for diagnosing CAD and had coronary angiography following the Tl-201 scans, were retrieved from the nuclear medicine databases in Changhua Christian Hospital. Table 1 shows the clinical characteristics of the enrolled patients. According to the coronary angiography of these patients, 57 did not have significant stenosis ($\geq 70\%$) in any coronary artery, 32 had $\geq 70\%$ stenosis in one of the coronary arteries, 36 had $\geq 70\%$ stenosis in two of the coronary arteries, and 19 had $\geq 70\%$ stenosis in all three coronary arteries, respectively. Except for more diabetes and history of myocardial infarction (MI) in patients with CAD, no significant differences were noted regarding the age, gender, hypertension, hyperlipidemia, smoking, family history of CAD, history of percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass graft (CABG). The study protocol was approved by the Institutional Review Board of Changhua Christian Hospital.

Imaging Protocol

Patients fasted at least 4 hours and were asked to abstain from caffeine-containing foods, beverages, and medications containing methylxanthine for 24 hours. Dipyridamole was administered intravenously at a rate of $0.14 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{minute}^{-1}$ for 4 minutes. 111 MBq of Tl-201 was then injected 3 minutes after the end of the dipyridamole infusion. Blood pressure and heart rate were recorded every minute. Aminophylline was given for patients suffering from severe adverse effects after dipyridamole stress, such as chest pain, dyspnea, nausea, vomiting, severe bradycardia (heart rate less than 40 bpm), 2nd or 3rd degree atrioventricular block, ST depression, or frequent premature ventricular contractions. As shown in Table 1, 16%–32% of patients suffered from severe adverse effects needing aminophylline for relieving the discomfort in different CAD groups, but there was no significant difference regarding the frequency or the dose of used aminophylline between the groups.

Stress and rest acquisitions started 5–10 minutes and 4 hours after Tl-201 injection in a supine position. No rest re-injection of Tl-201 was done. A dual-head gamma camera (Millennium MG, GE, Haifa, Israel) equipped with a low-energy general-purpose collimator was used. Thirty-two projections, with 70 seconds of data collection per projection, were obtained over a 180° arc extending from the 45° right anterior oblique to the 45° left posterior oblique position. A 20% window was centered over the 72 and 167 keV Tl-201 photopeaks. The acquisition was synchronized with ECG with an acceptance window of 100%, and each projection was divided into eight images per cardiac cycle. The projection images were acquired into 64×64 matrices with a 1.45 acquisition zoom and were reconstructed by filtered back projection with a Butterworth filter (order = 10 and cut-off frequency = $0.4 \text{ cycle}\cdot\text{pixel}^{-1}$).

Table 1. Clinical characteristics of the enrolled patients

	0-vessel CAD (N = 57)	1-vessel CAD (N = 32)	2-vessel CAD (N = 36)	3-vessel CAD (N = 19)	P value
Age	62 ± 12	64 ± 11	67 ± 11	65 ± 9	NS
Male	38 (67%)	20 (65%)	30 (81%)	16 (84%)	NS
Hypertension	37 (65%)	24 (77%)	18 (49%)	16 (84%)	NS
Diabetes	11 (19%)	10 (32%)	13 (35%)	11 (58%)	.016
Hyperlipidemia	24 (42%)	17 (55%)	23 (62%)	14 (74%)	NS
Smoking	24 (42%)	13 (42%)	17 (46%)	9 (47%)	NS
Family history	6 (11%)	3 (10%)	3 (8%)	2 (11%)	NS
Myocardial infarction	1 (2%)	4 (13%)	3 (8%)	4 (21%)	.044
PTCA	4 (7%)	6 (19%)	7 (19%)	1 (5%)	NS
CABG	0 (0)	0 (0)	2 (5%)	0 (0)	NS
Aminophylline use	14 (25%)	5 (16%)	12 (32%)	5 (26%)	NS
Aminophylline dose (mg)	60.7 ± 6.7	62.5 ± 0	77.1 ± 24.9	62.5 ± 0	NS

CAD, coronary artery disease; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft.

Image Analysis

The perfusion images were displayed in the short-axis, vertical long-axis, and horizontal long-axis views. The LV was divided into 17 segments and all segments were scored with a 5-point scale (0 = normal, 1 = mildly reduced, 2 = moderately reduced, 3 = severely reduced, and 4 = absent uptake) by two experienced observers in consensus. The summed stress score (SSS) and summed rest score (SRS) were obtained by the sum of the scores of 17 segments on stress and rest images. The summed difference score (SDS) was defined as the difference of SSS and SRS. The patients were then divided into normal group, infarct group, and ischemia group as previously described.¹³ The 17 segments were classified into three vascular territories: left anterior descending artery (LAD) for apex and anterior wall, left circumflex artery (LCX) for lateral wall, and right coronary artery (RCA) for inferior wall. The perfusion of an individual territory was classified as abnormal when at least 1 point of abnormality on consecutive 2 or more segments on stress images.

The gated data were processed with completely automated software (QGS 3.0; Cedars-Sinai Medical Center, Los Angeles, CA) to calculate LVEF and LV volumes. Our previous work assessed the repeatability of LVEF measurements by TI-201 gated SPECT,¹⁴ and an increase or decrease of 6% or greater between the post-stress and rest gated SPECT studies was considered significant. For regional wall motion analysis, SSS, SRS, and SDS for RWA were calculated as our previous study.¹⁵ SDS for RWA greater than 2 was considered to indicate the presence of reversible RWAs (RRWA).

For dyssynchrony assessment, all of the SPECT images were transferred to Emory University by phase analysis,⁷ which was done blinded from the angiographic results. The phase analysis technique calculated a phase value for each

sampled region (>600 sampled regions for the entire LV), which represented the onset of mechanical contraction of the region. The SD of all phase values and bandwidth of the phase histogram characterized LV global dyssynchrony.⁷ Furthermore, phase SD was calculated for the three coronary territories, respectively, as demonstrated in Figure 1. The global and territorial dyssynchrony parameters were then compared between the stress and rest images in the four patient groups classified according to the angiographic results (no significant stenosis, 1-vessel disease, 2-vessel disease, and 3-vessel disease), respectively.

According to a previous study that measured the repeatability of the phase analysis technique,¹⁶ the SD of phase SD between two serial scans was 2.6°. With a *z* score of 1.65, a difference of 4.3° in phase SD was considered statistically significant between two scans. Using this criterion, in this study an increase in phase SD in the coronary territories from rest to stress was considered a significant deterioration of territorial synchrony and used as an indication of significant stenosis in the corresponding coronary artery. The incremental diagnostic value of the territorial dyssynchrony assessment over the visual interpretation was evaluated in the patients with 3-vessel disease.

Statistical Analysis

Phase SD was compared among stress and rest images using paired *t* test. Unpaired *t* test with unequal variance was used to compare phase SD among the groups. χ^2 test was used to compare the proportions of the patients with 3-vessel angiographic CAD, who were detected using various methods in Figure 4. *P* < .05 was considered statistically significant.

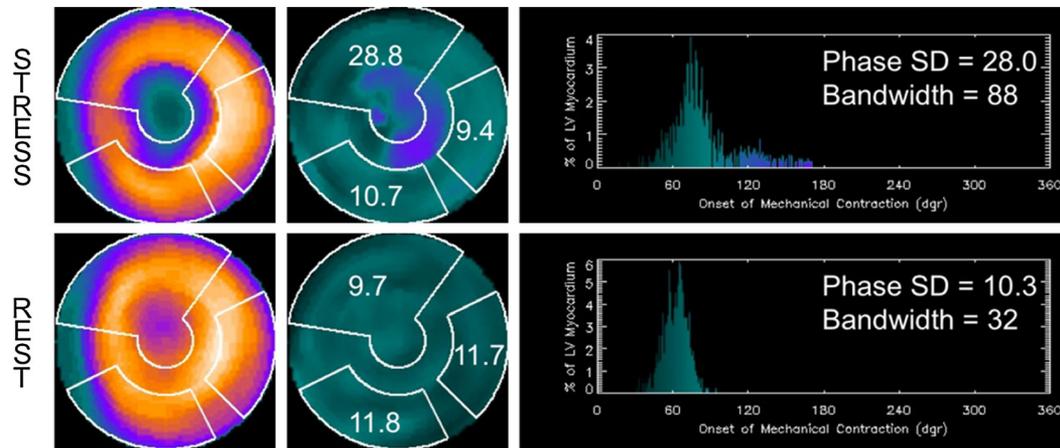


Figure 1. Dyssynchrony assessment for the entire LV (phase standard deviation [SD] and histogram bandwidth) and coronary territories (phase SD in the territories). This patient had a 100% stenosis in the mid left anterior descending artery (LAD) according to the coronary angiography. The global dyssynchrony parameters (phase SD and histogram bandwidth) and LAD phase SD deteriorated from rest to early post-stress. Such deterioration was due to the delayed contraction in the ischemic region.

RESULTS

Table 2 shows the global dyssynchrony parameters in the patient groups. In general, the patient groups with more severe angiographic CAD had more dyssynchrony than the patient groups with less angiographic CAD. However, only the patient groups with 2-vessel disease and with 3-vessel disease had significantly more global dyssynchrony than the patient group without $\geq 70\%$ stenosis at stress. When comparing the stress and rest dyssynchrony, two opposite trends were observed. In the patient group without $\geq 70\%$ stenosis, stress images showed significantly less dyssynchrony than the rest images. On the contrary, in the patient groups with 2-vessel disease and with 3-vessel disease the stress images showed significantly more dyssynchrony than the rest images. This finding demonstrated myocardial stunning in the patients with severe and extensive CAD.

Table 3 shows the global and territorial dyssynchrony parameters in the patient group with 2-vessel disease. Subgroup analysis showed that the patients with LAD $\geq 70\%$ stenosis had significant more dyssynchrony (both globally and territorially in LAD) at stress than at rest. Such finding was not observed in the patients without LAD $\geq 70\%$ stenosis. This finding indicated that LAD stenosis had higher impact on dyssynchrony than the stenosis in other coronary arteries.

Table 4 shows the global and territorial dyssynchrony parameters in the patient group with 3-vessel angiographic CAD. The stress images showed significantly more dyssynchrony for the entire LV and for the coronary territories than the rest images.

Figure 2 shows phase SD in the patients with normal perfusion (N = 71), infarct (N = 31), and ischemia (N = 42). From rest to stress, phase SD

Table 2. Dyssynchrony assessment for the entire LV

	Phase SD		Histogram bandwidth	
	Stress	Rest	Stress	Rest
0-vessel CAD (N = 57)	17.2 ± 10.3* [^]	19.1 ± 10.9*	53.2 ± 32.9* [^]	64.1 ± 32.7*
1-vessel CAD (N = 32)	18.4 ± 8.9	20.3 ± 11.9	57.7 ± 32.3	61.7 ± 25.1
2-vessel CAD (N = 36)	25.3 ± 13.8* [^]	22.2 ± 14.2*	79.0 ± 48.1* [^]	70.6 ± 49.8*
3-vessel CAD (N = 19)	29.5 ± 21.2* [^]	24.2 ± 17.4*	88.8 ± 78.9 [^]	83.2 ± 59.8

CAD, coronary artery disease; SD, standard deviation.

*P < .05 when comparing the stress and rest dyssynchrony parameters in the patient groups using the paired t test.

[^]P < .05 when comparing the dyssynchrony parameters against the patient group with no $\geq 70\%$ stenosis using unpaired t test with unequal variance.

Table 3. Dyssynchrony assessment in the patients with 2-vessel disease

	w/LAD ≥ 70% Stenosis (N = 29)		w/o LAD ≥ 70% Stenosis (N = 7)	
	Stress	Rest	Stress	Rest
Entire LV	25.2 ± 12.3*	21.5 ± 12.3*	25.7 ± 20.6	25.3 ± 21.5
LAD	24.7 ± 15.2*	20.2 ± 12.3*	21.8 ± 15.3	24.3 ± 17.7
LCX	19.6 ± 9.8	20.6 ± 8.7	28.2 ± 27.3	27.7 ± 33.4
RCA	24.0 ± 12.4	24.2 ± 11.4	28.2 ± 21.3	23.7 ± 16.3

LV, left ventricle; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.
*P < .01 when comparing the stress and rest dyssynchrony parameters using the paired t test.

Table 4. Dyssynchrony assessment in the patients with 3-vessel disease

	Stress phase SD	Rest phase SD
Entire LV	29.5 ± 21.2*	24.2 ± 17.4*
LAD	27.5 ± 19.7*	21.3 ± 15.7*
LCX	28.6 ± 26.8*	24.2 ± 20.8*
RCA	30.4 ± 14.8*	25.1 ± 12.9*

SD, standard deviation; LV, left ventricle; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.
*P < .01 when comparing the stress and rest dyssynchrony parameters using the paired t test.

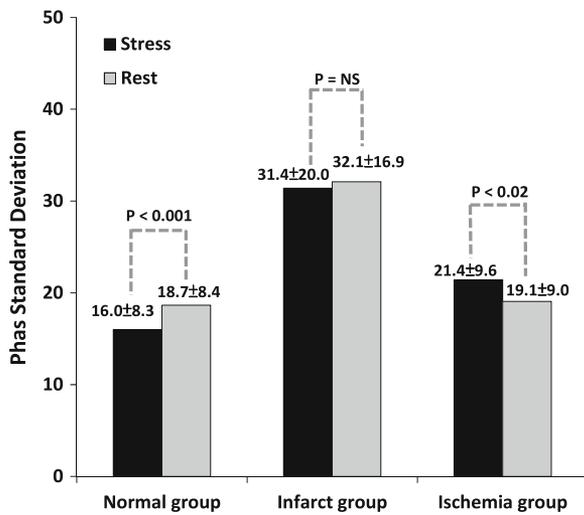


Figure 2. Stress and rest phase standard deviation (SD) in the patients with normal perfusion, infarct, and ischemia.

significantly reduced in the patients with normal perfusion, but significantly increased in the patients with ischemia. This result also demonstrated myocardial stunning in the CAD patients and confirmed the finding of our previous study.¹³ However, a weak correlation

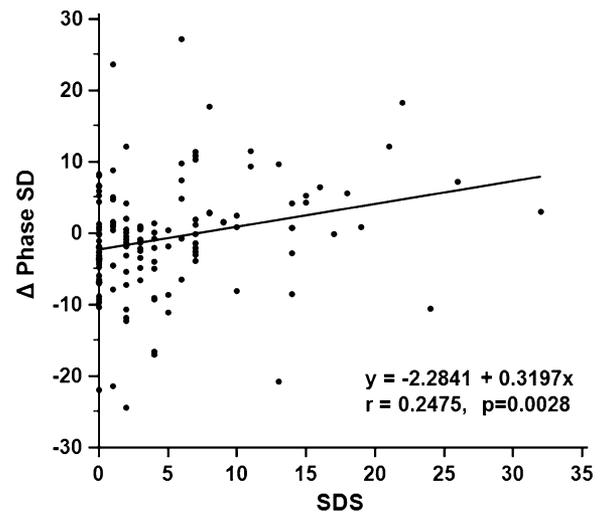


Figure 3. The correlations of phase standard deviation (SD) change from stress to rest and summed difference score (SDS).

was found between phase SD change from stress to rest and SDS ($r = 0.2475$, $P = .0028$), as shown in Figure 3.

Figure 4 shows the diagnostic results in the patients with 3-vessel angiographic CAD by the visual interpretation noted in the nuclear medicine databases, visual interpretation plus LVEF changes, visual interpretation plus regional wall motion assessment, territorial dyssynchrony assessment, and visual interpretation plus territorial dyssynchrony assessment, respectively. Significantly more patients with 3-vessel angiographic CAD were correctly classified as 3-vessel disease when combining both visual interpretation and territorial dyssynchrony assessment than visual interpretation alone ($P < .001$). Figure 4 also shows a promising trend that the incremental value of the territorial dyssynchrony assessment in the diagnosis of 3-vessel angiographic CAD over visual interpretation was higher than both LVEF changes and regional wall motion assessment.

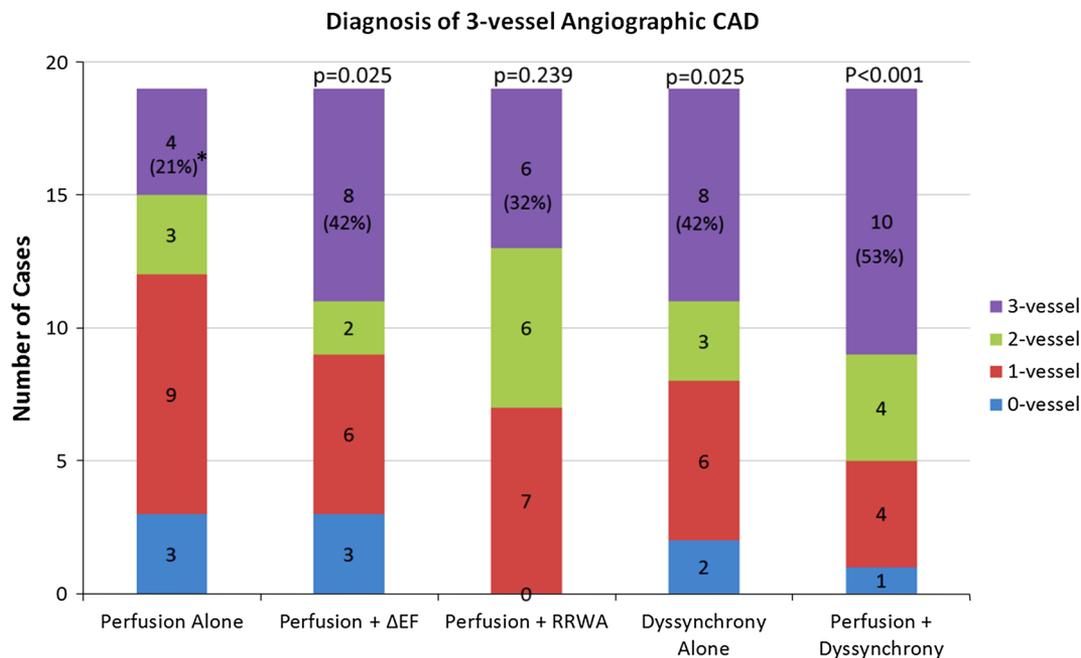


Figure 4. The incremental value of the territorial dyssynchrony assessment over the visual interpretation of the perfusion images in the diagnosis of 3-vessel angiographic coronary artery disease (CAD). *The proportions of the patients with 3-vessel angiographic CAD, who were detected by the methods. The *P* values were calculated by comparing against perfusion alone using χ^2 test.

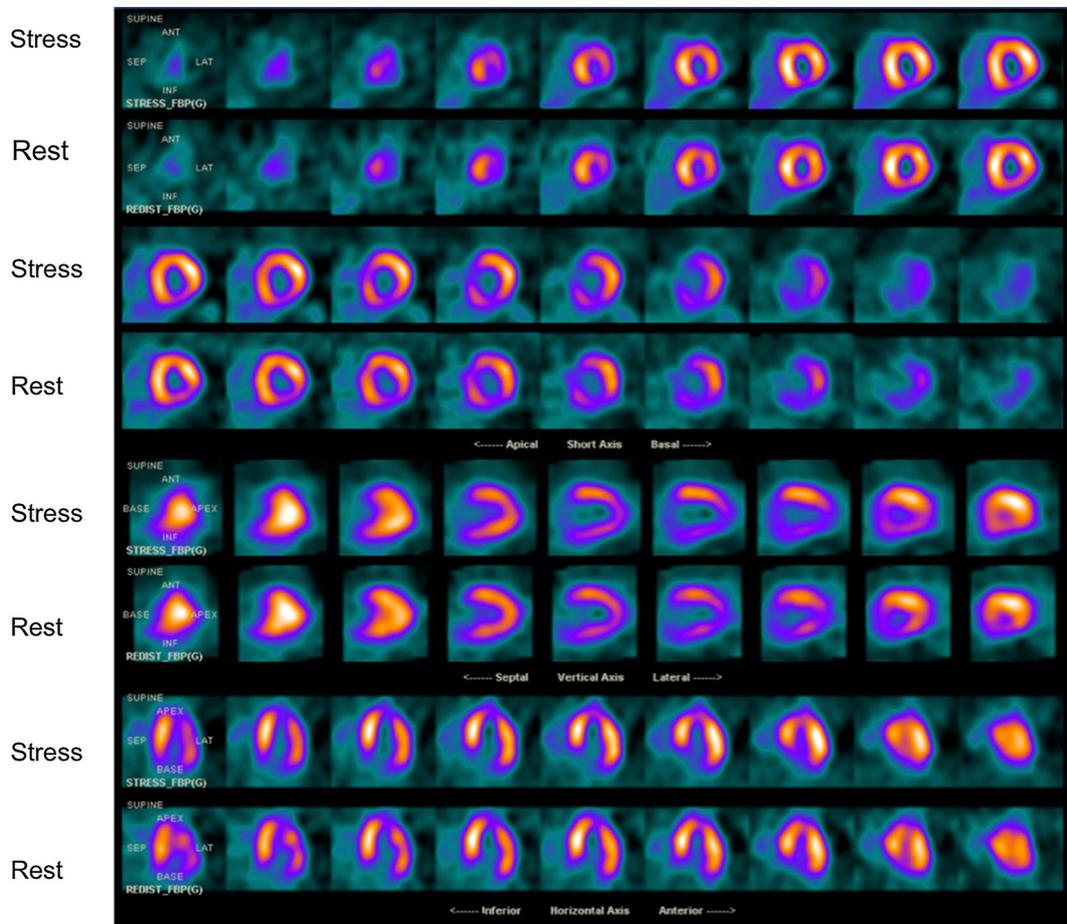
DISCUSSION

This study was the first study to demonstrate the relation between early post-stress dyssynchrony and angiographic CAD using TI-201 gated SPECT MPI. The main finding of this study was that the patients with severe multi-vessel CAD had significantly more global and territorial dyssynchrony at stress than at rest. On the contrary, the patients without significant stenosis in any coronary arteries had significantly less dyssynchrony at stress than at rest. Such different dyssynchrony pattern clearly demonstrated myocardial stunning in the patients with severe multi-vessel CAD. In addition, regional phase analysis was used in two previous studies to measure the site of latest mechanical activation as the optimal LV lead positions for cardiac resynchronization therapy (CRT) in heart failure patients.^{17,18} Those two studies showed that CRT response improved when pacing the regions with delayed contraction as measured by regional phase analysis of gated SPECT MPI images. This study was the first study to use regional phase analysis to measure delayed contraction in coronary territories in CAD patients.

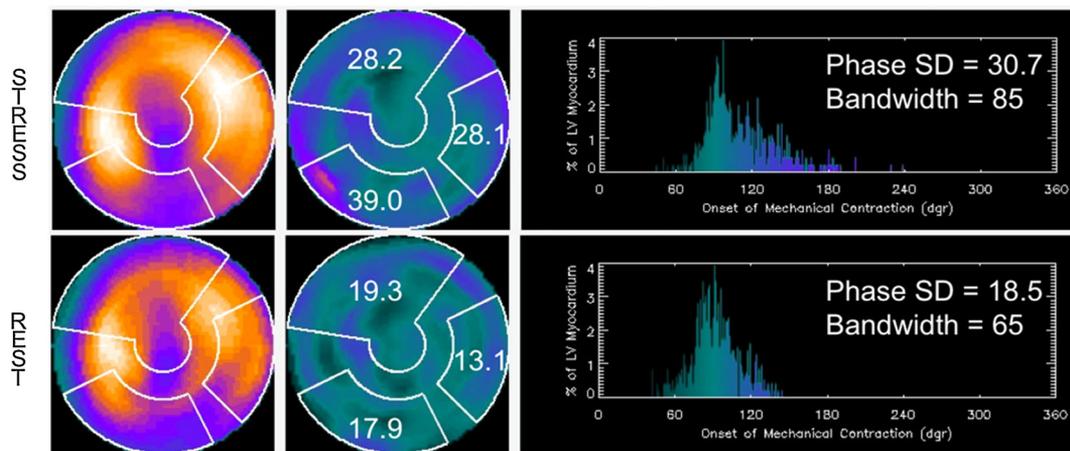
The conventional stress/rest MPI provided relative perfusion information of different vascular territories of the LV, thus might underestimate the extent and severity of ischemia for patients with relatively balanced

perfusion abnormality in multi-vessel disease. According to the study of Berman et al,¹⁹ MPI might underestimate the extent of ischemia in about 20-50% of multi-vessel CAD patients. Therefore, the measurement of myocardial stunning can assist in the diagnosis of multi-vessel CAD patients, especially the ones with balanced ischemia in 3-vessel disease.

Figure 4 showed that the territorial dyssynchrony assessment had an incremental value over the visual interpretation of the conventional stress/rest perfusion images in the diagnosis of 3-vessel angiographic CAD. Figure 5 shows a patient example to demonstrate such incremental diagnostic value of the territorial dyssynchrony assessment in balanced 3-vessel disease. The perfusion images of this patient showed balanced perfusion distribution at both stress and rest, which resulted in small perfusion defects (SSS = 6, SRS = 4). The SDS in the LAD, LCX, and RCA territories were 1, 0, and 1, respectively. Visual interpretation noted only mild grade of perfusion abnormality in the apex and inferior wall. For TI-201 images, such an abnormality was not uncommon due to attenuation artifact,²⁰ thus the perfusion images were considered as an equivocal finding of CAD. The post-stress and rest LVEF was 53% and 54%, respectively, and the transient ischemic dilation (TID) ratio was 1.01. Based on our previous



A Perfusion images at stress and at rest



B LV global and territorial dyssynchrony assessment at stress and at rest

Figure 5. An example patient with a balanced 3-vessel disease. **(A)** The perfusion images revealed only mild grade of perfusion abnormality with partial reversibility in apex and inferior. **(B)** Perfusion polar map (left column), phase polar map (middle column) and phase histogram (right column). The phase analysis revealed remarkable deterioration in global and territorial synchrony from rest to stress.

study, the case should be considered to have severe CAD only when TID ratio ≥ 1.19 ¹⁴ or stress-induced worsening of LVEF $\geq 6\%$.¹⁵ Noteworthy, this patient had remarkable deterioration in global and territorial synchrony from rest to stress. According to the coronary angiography this patient had LAD stenosis 70%, LCX stenosis 80%, RCA stenosis 70%, respectively.

Another finding of this study was that LAD stenosis had higher impact on dyssynchrony than the stenosis in other coronary arteries, as shown in the patient group with 2-vessel disease (Table 3). The reason might be that LAD generally supplies blood to a larger LV territory than other vessels. However, the number of patients in Table 3 was small, so such finding needs to be confirmed in a larger population.

In this study, patients underwent dipyridamole stress instead of exercise stress. Although perfusion abnormalities during dipyridamole stress reflect heterogeneity of coronary reserve, which may not be considered as true ischemia. Nevertheless, ischemia sometimes does occur under dipyridamole stress and results in ischemic stunning. Our previous studies of TI-201 gated SPECT MPI found that dipyridamole-induced stunning, manifested as LVEF worsening during dipyridamole stress, was a highly specific marker of significant CAD.^{14,15,21} In a study by Lee et al,²² dipyridamole-induced reversible regional wall-motion abnormalities were present in one half of the patients with CAD on 1-hour post-stress Tc-99m sestamibi gated SPECT images. With Rb-82 PET and dipyridamole or adenosine stress, Dorbala et al²³ also showed reduced LVEF greater than 5% in patients with multi-vessel CAD.

The main limitation of this study was the use of TI-201 tracer. TI-201 SPECT MPI usually has higher noise and poorer image quality than Tc-99m SPECT MPI. Therefore, this study used a prolonged acquisition protocol (70 second·projection⁻¹) to increase the count density in the images. TI-201 SPECT MPI started the acquisition within 10-minutes post injection, representing early post-stress. Therefore, it can measure myocardial stunning better than the Tc-99m SPECT, which usually acquires images late post-stress. Noteworthy, Rb-82 PET acquires peak-stress images and has better image quality than TI-201 SPECT; therefore, the findings of this study may become more prominent if using Rb-82 PET. Finally, the image analysis in this study was done in the images retrieved from the nuclear medicine databases, not prospectively enrolled patients. Therefore, the findings of this study need to be validated prospectively, especially for the purpose of establishing the incremental diagnostic value of the dyssynchrony assessment over the perfusion assessment in multi-vessel CAD.

In conclusion, the patients with severe multi-vessel angiographic CAD had significantly more global and territorial dyssynchrony at early post-stress than at rest, as assessed by TI-201 gated SPECT MPI. Such quantitative measures of myocardial stunning showed an incremental value over the visual interpretation of the conventional perfusion images in the diagnosis of 3-vessel disease.

NEW KNOWLEDGE GAINED

Early post-stress dyssynchrony, as measured by phase analysis of TI-201 gated SPECT MPI, characterizes ischemia-induced myocardial stunning and is related to the extent of angiographic CAD.

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Disclosure

Dr Ji Chen receives royalties from the sale of Emory Cardiac Toolbox with SyncTool. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict-of-interest practice.

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