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ORIGINAL ARTICLE

Stress-induced myocardial ischemia is associated with early post-stress left ventricular mechanical dyssynchrony as assessed by phase analysis of ^{201}Tl gated SPECT myocardial perfusion imaging

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Abstract
Purpose In ^{201}Tl SPECT myocardial perfusion imaging (MPI) data are acquired shortly after the stress injection to assess early post-stress left ventricle (LV) function. The purpose of this study was to use ^{201}Tl SPECT MPI to investigate whether stress-induced myocardial ischemia is associated with LV mechanical dyssynchrony.
Methods Enrolled in the study were 75 patients who were referred for dipyridamole stress and rest ^{201}Tl gated SPECT MPI. The early post-stress scan was started 5 min after injection, and followed by the rest scan 4 h later. The patients were divided into three groups: ischemia group (N=25, summed stress score, SSS, ≥5, summed rest score, SRS, <5), infarct group (N=16, SSS ≥5, SRS ≥5) and normal group (N=34, SSS <5, SRS <5). LV dyssynchrony parameters were calculated by phase analysis, and compared between the stress and rest images.
Results In the ischemia group, LV dyssynchrony was significantly larger during stress than during rest. On the contrary, LV dyssynchrony during stress was significantly smaller than during rest in the normal and infarct groups. LV dyssynchrony during rest was significantly larger in the infarct group than in the normal and ischemia groups. There were no significant differences in LV dyssynchrony during rest between the normal and ischemia groups.
Conclusion Stress-induced myocardial ischemia caused dyssynchronous contraction in the ischemic region, leading to a deterioration in LV synchrony. Normal myocardium had more synchronous contraction during stress. The different dyssynchrony pattern between ischemic and normal myocardium early post-stress may aid the diagnosis of coronary artery disease using ^{201}Tl gated SPECT MPI.

Keywords Thallium-201 · Gated SPECT · Left-ventricular dyssynchrony · Myocardial ischemia

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Introduction

Phase analysis has been developed for measuring left-ventricular (LV) dyssynchrony from gated SPECT myocardial perfusion imaging (MPI) [1]. It has been shown that quantitative indices given by phase analysis, such as phase standard deviation (PSD) and phase histogram bandwidth (PHB), correlate well with LV dyssynchrony measured by tissue Doppler imaging [2–4]. Most importantly, these indices have been shown to predict response to cardiac resynchronization

Table 1 Clinical characteristics

Characteristic	Group			*p* value
	Normal (*n*=34)	Ischemia (*n*=25)	Infarct (*n*=16)	
Age (years, mean±SD)	61±10.2	69±10.7	67±10.0	0.03
Male	26 (77 %)	16 (64 %)	9 (56 %)	NS
Hypertension	21 (62 %)	22 (88 %)	14 (88 %)	0.032
Diabetes	7 (21 %)	9 (36 %)	6 (38 %)	NS
Hyperlipidemia	16 (47 %)	17 (68 %)	11 (69 %)	NS
Smoking	12 (35 %)	5 (20 %)	5 (31 %)	NS
Family history	10 (29 %)	4 (16 %)	3 (19 %)	NS

NS not significant.

therapy in patients with heart failure [5]. As the phase analysis technique can be applied to conventional gated SPECT MPI data with good reproducibility [6] and repeatability [7], it shows promise to become a standard, widespread nuclear cardiology tool in coronary artery disease (CAD), heart failure, and cardiac electrophysiology.

All of the above studies were done using ^{99m}Tc-sestamibi or tetrofosmin as the radiotracer. As ^{99m}Tc-sestamibi or tetrofosmin gated SPECT MPI data are usually acquired about 1 h after injection, they represent post-stress function, which is close to resting function. A study using ^{99m}Tc-sestamibi SPECT MPI has shown that the presence of even large reversible defects does not alter LV dyssynchrony from rest to stress [8]. As ^{201}Tl gated SPECT MPI data are acquired close to peak stress (usually within 5 min of injection), they offer the opportunity to investigate stress-induced changes in LV function and dyssynchrony. Our group have previously shown that stress-induced changes in LV ejection fraction (LVEF) are a valuable nonperfusion marker of significant CAD [9–11] and related to transient ischemic dilation [12]. The purpose of this study was to use ^{201}Tl gated SPECT MPI to investigate whether stress-induced myocardial ischemia is associated with LV mechanical dyssynchrony.

Table 2 LV perfusion and function parameters in the normal, ischemia and infarct groups. Values are means±SD

	Normal group	Ischemia group	Infarct group
Summed stress score	1.0±1.5	18.3±7.5	17.7±6.3
Summed rest score	0.9±1.7	1.4±1.8	9.3±3.9
Summed difference score	0.1±2.0	16.9±6.5	8.4±4.6
Ejection fraction			
Stress	82.8±5.6	69.2±10.4	59.0±19.6
Rest	78.9±7.9	72.6±9.4	61.2±17.4
p value	0.02	NS	NS
Phase standard deviation			
Stress	15.9±5.0	22.0±7.8	30.4±15.1
Rest	19.0±4.2	17.0±4.8	37.9±17.5
p value	<0.001	<0.001	0.0014
Phase histogram bandwidth			
Stress	45.5±11.2	66.7±21.1	93.3±52.8
Rest	57.4±11.5	54.5±15.3	113.8±65.0
p value	<0.001	0.0045	0.0097

Materials and methods

Patient population

Enrolled in this prospective study were 75 consecutive patients with known or suspected CAD referred for dipyridamole stress/rest gated ^{201}Tl gated SPECT MPI. Patients with a low likelihood of CAD, normal LV function, no heart failure symptoms, no electrocardiogram abnormalities, and normal perfusion images on MPI were considered normal controls. Patients with evidence of myocardial ischemia and myocardial infarction were also included. This study was approved by the Institutional Review Board of Chang Bing Show Chwan Memorial Hospital.

^{201}Tl gated SPECT MPI

Patients fasted for at least 4 h and were asked to abstain from caffeine-containing foods, beverages and medications containing methylxanthine for 24 h. Dipyridamole was administered intravenously at a rate of 0.14 mg/kg/min over 4 min. ^{201}Tl (111 MBq) was then injected 3 min after the end of the dipyridamole infusion. Blood pressure and heart rate were recorded every minute. Aminophylline was given to seven patients (9 %) suffering from severe adverse effects after dipyridamole stress, including chest pain, dyspnea, nausea, vomiting, severe bradycardia (heart rate less than 40 bpm), second or third degree atrioventricular block, ST depression, and frequent premature ventricular contractions.

Stress and rest scans were acquired with the patient in a supine position starting 5–10 min and 4 h after ^{201}Tl injection. ^{201}Tl was not reinjected for the rest scan. A dual-head gamma camera (Symbia T2; Siemens Medical Solutions, Knoxville,

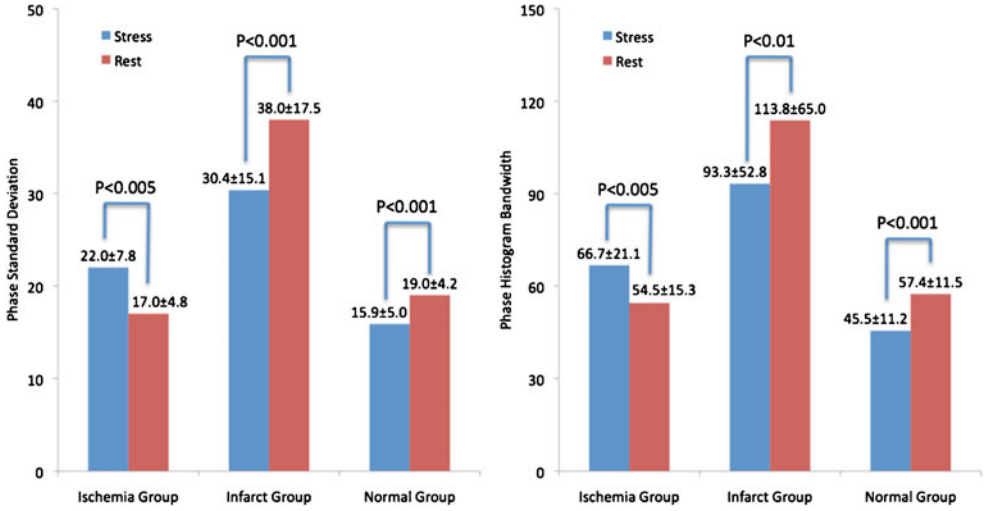

Fig. 1 LV dyssynchrony early post-stress and during rest in patients with ischemic, infarcted, or normal myocardium

TN) equipped with a low-energy high-resolution collimator was used. The acquisition comprised 32 projections, with 50 s of data collection per projection, 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 ^{201}Tl photopeaks. The acquisition was synchronized electrocardiographically 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, cut-off frequency 0.5 cycles per pixel).

Image analysis

The gated SPECT MPI data were analyzed with the Emory Cardiac Toolbox (ECTb). For perfusion analysis, the LV was divided into 17 segments, and all segments were scored automatically by ECTb using its enhanced thallium normal database on a five-point scale (0, normal; 1, mildly reduced; 2, moderately reduced; 3, severely reduced; and 4, absent uptake). Summed stress scores (SSS) and summed rest scores (SRS) were the sum of the scores of the 17 segments on stress and rest images. Summed difference scores (SDS) were then calculated as SSS minus SRS. The patients were then divided into three groups: (1) normal group, with no or minor defects (SSS <5, SRS <5); ischemia group, with significant reversible defects (SSS ≥5, SRS <5); and infarct group, with significant fixed defects (SSS ≥5, SRS ≥5). LV dyssynchrony parameters, PSD and PHB, were then calculated and compared between the stress and rest images.

Statistical analysis

LV global dyssynchrony (PSD and PHB) were compared among stress and rest images using a paired *t*-test. The PSD and PHB between different groups of patients were compared using an unpaired *t*-test with unequal variance. Noncontinuous variables were expressed as frequency and percentage and tested by a chi-squared test. A p value lower than 0.05 was considered statistically significant.

Results

Of the 75 patients, 34, 25 and 16 were allocated to the normal, ischemia and infarct groups, respectively. Their clinical characteristics are shown in Table 1. Patients in the normal group were younger and had a lower frequency of hypertension. No significant difference was noted among the three groups in terms of gender, diabetes, hyperlipidemia, smoking or family history.

The parameters of LV perfusion and function are shown in Table 2. LVEF during stress in the normal group was significantly higher than during rest. On the contrary, LVEF during stress in the ischemia and infarct groups was lower than during rest; however, the differences did not reach statistical significance.

LV dyssynchrony parameters were summarized in Fig. 1. Both PSD and PHB were significantly reduced during stress than during rest in both normal and infarct groups, but increased during stress than during rest in the ischemia group. Both PSD and PHB during rest were significantly larger in the infarct group than that in the normal and ischemia groups (both $p<0.001$). There were no significant differences in LV dyssynchrony during rest between the normal and ischemia groups. Fig. 2 shows an example for each group, respectively.

The changes in the LV dyssynchrony parameters from rest to stress (ΔPSD, ΔPHB) were compared with SDS and the changes in LVEF (ΔLVEF). The correlation coefficients are shown in Table 3. There were weak relationships between ΔPSD/ΔPHB and SDS and between ΔPSD/ΔPHB and ΔLVEF in the entire population and in the ischemia group, respectively.

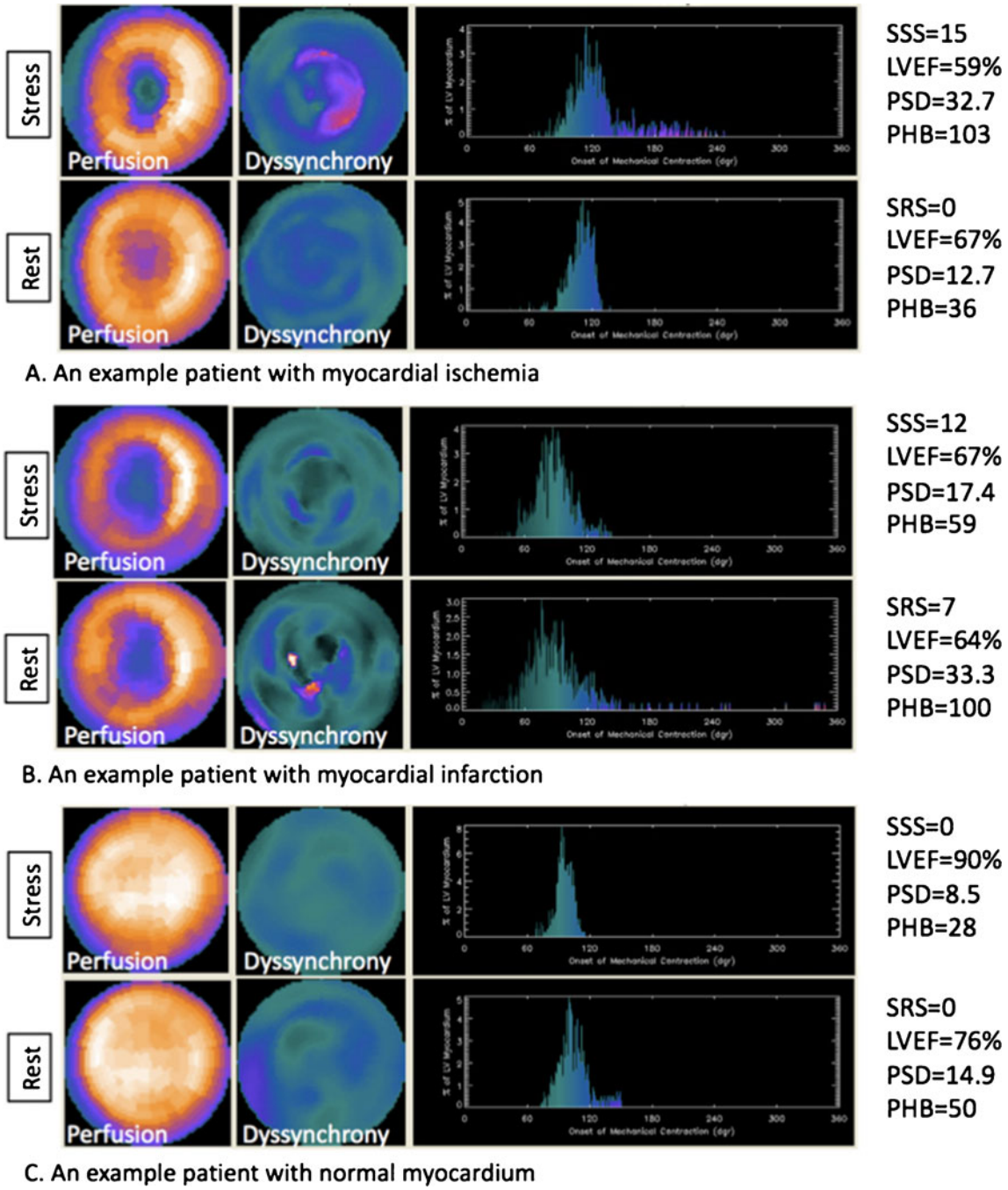

Fig. 2 Gated SPECT MPI images in example patients with ischemic (**a**), infarcted (**b**) and normal (**c**) myocardium

Discussion

This is the first study using ^{201}Tl gated SPECT MPI to demonstrate the different dyssynchrony patterns in ischemic, infarcted, and normal myocardium in response to pharmacological stress. LV global dyssynchrony was significantly larger early post-stress than during rest in the ischemic group, but significantly larger in the normal and infarct groups. These findings indicated that stress caused more dyssynchronous contraction in ischemic myocardium and more synchronous contraction in normal myocardium. Although delayed contraction persisted in infarcted myocardium during both stress and rest, stress caused more synchronous contraction of the rest normal myocardium, and thus resulted in less LV global dyssynchrony in the infarct group.

Dyssynchronous contraction in stress-induced ischemia is associated with stress-induced stunning, which may be reflected as stress-induced worsening in LVEF and/or

Table 3 LV perfusion and function parameters in the normal, ischemia and infarct groups

Comparison	Entire population (n=75)		Normal group (n=34)		Ischemia group (n=25)		Infarct group (n=16)	
	Correlation coefficient	p value	Correlation coefficient	p value	Correlation coefficient	p value	Correlation coefficient	p value
ΔPSD vs. SDS	0.45	<0.0001	0.06	NS	0.34	NS	0.03	NS
ΔPHB vs. SDS	0.44	0.0001	0.08	NS	0.08	NS	0.30	NS
ΔPSD vs. ΔLVEF	−0.24	0.0345	−0.01	NS	−0.34	NS	0.04	NS
ΔPHB vs. ΔLVEF	−0.23	0.0401	−0.04	NS	−0.36	NS	0.14	NS

NS not significant.

regional wall motion abnormality as shown in our previous studies using ^{201}Tl gated SPECT MPI [9, 10, 12]. In this study, however, the early post-stress decrease in LVEF in the ischemia group was not statistically significant, despite weak correlations with stress-induced dyssynchrony. It is noteworthy that a recent study showed that the presence of a reversible perfusion defect did not alter the parameters of LV dyssynchrony when measured using ^{99m}Tc-sestamibi gated SPECT MPI [8]. As mentioned in the report of that study, the perfusion defects shown on the ^{99m}Tc SPECT images were a reflection of myocardial blood flow at the time of tracer injection, but the wall motion, LVEF, and dyssynchrony were derived from the gated images that were acquired at the time of imaging, usually 45–60 min after the start of stress. Since ^{201}Tl gated SPECT MPI acquires stress images at 5–10 min after the start of stress, this study for the first time demonstrated that assessment of stress-induced dyssynchrony in ischemic myocardium is feasible by ^{201}Tl gated SPECT MPI. Moreover, the degrees of stress-induced dyssynchrony as assessed by phase analysis of ^{201}Tl gated SPECT MPI were found to moderately but significantly correlate with SDS (PSD vs. SDS: r=0.45, p<0.0001; PHB vs. SDS: r=0.44, p=0.0001). These correlations are interesting, as these variables measure two different processes (function vs. perfusion). In addition, our finding that stress caused more synchronous contraction in normal myocardium is consistent with a recent report using ^{82}Rb gated PET [13], which showed that LV dyssynchrony is reduced when derived from peak stress versus rest in patients with normal myocardium.

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, ischemia sometimes does occur and results in ischemic stunning. In a study by Lee et al. [14], dipyridamole-induced reversible regional abnormalities in wall motion were present in one-half of patients with CAD on ^{99m}Tc-sestamibi gated SPECT images acquired 1 h after the start of stress. Our previous study also found that dipyridamole-induced stunning, manifested as LVEF worsening during dipyridamole stress, was a highly specific marker of significant CAD [9, 10]. The exact mechanism underlying vasodilator-induced myocardial ischemia is still not well understood. The most widely accepted explanation is the coronary steal phenomenon [15]. In the myocardial segments supplied by stenosed vessels, stress perfusion did not increase as much as that of normal vessels and was even less than resting perfusion. In addition, most of the patients had an increased heart rate after vasodilator stress as a result of a reflex sympathetic response, which might have caused a certain grade of increased oxygen demand that exaggerated the coronary steal-related ischemia.

Clinical implications

Comparison of LV dyssynchrony early post-stress vs. during rest by ^{201}Tl gated SPECT MPI can help differentiate myocardial ischemia from normal myocardium and myocardial infarction. Assessment of stress-induced dyssynchrony can provide additional nonperfusion markers of CAD that may have an incremental value in the diagnosis of CAD using ^{201}Tl gated SPECT MPI.

Study limitations

This was a proof-of-concept study, whose findings need to be prospectively validated in a larger study. Specifically, the clinical value of stress-induced dyssynchrony assessed by ^{201}Tl gated SPECT MPI in the diagnosis of CAD needs to be validated against coronary angiography. Such validation would require an advanced phase analysis tool to assess not only LV global dyssynchrony but also dyssynchrony in coronary territories. Phase analysis was initially developed and validated with ^{99m}Tc-labeled tracers [1–5]. In general, ^{201}Tl gated SPECT MPI has poorer counting statistics than ^{99m}Tc gated SPECT MPI. Nevertheless, the average signal-to-noise ratios (SNR) in the perfusion defects in this study were 35.3±10.9 and 30.2±12.5 in the ischemia group and infarct group, respectively. Only one patient in the infarct group had a SNR below 12.0 (11.2), the threshold for

accurate phase analysis determined in a previous study [16]. The extent of perfusion defects alone did not seem to affect phase analysis, as long as the counts in the defects were sufficient, i.e. SNR greater than 12.0. ^{201}Tl gated SPECT MPI also has poorer spatial resolution than ^{99m}Tc gated SPECT, but ^{201}Tl gated SPECT MPI has been shown to produce comparable results in measuring LVEF and volumes to those produced by ^{99m}Tc gated SPECT MPI [17, 18]. Therefore, further investigation based on the accuracy of phase analysis of ^{201}Tl gated SPECT MPI is warranted.

Conclusion

This study demonstrated the different dyssynchrony patterns assessed by ^{201}Tl gated SPECT MPI early post-stress versus during rest in patients with ischemic, infarcted, and normal myocardium. Further study is warranted to assess the incremental value of stress-induced dyssynchrony over conventional assessment of ^{201}Tl gated SPECT MPI in the diagnosis of CAD.

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Conflicts of interest Dr. Ji Chen receives royalties from the sale of Emory 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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