Exercise-Induced Post-Ischemic Left Ventricular Delayed Relaxation or Diastolic Stunning

Is it a Reliable Marker in Detecting Coronary Artery Disease?

Katsuhisa Ishii, MD, Makoto Imai, MD, Tamaki Suyama, MD, Motoyoshi Maenaka, MD, Takahiro Nagai, MD, Masaki Kawanami, MD, Yutaka Seino, MD

Osaka, Japan

Objectives
The aim of this study was to determine whether post-ischemic left ventricular (LV) delayed relaxation could be detected by using strain imaging (SI) derived from 2-dimensional speckle-tracking echocardiography in patients with stable effort angina.

Background
Regional LV delayed relaxation during early diastole is a sensitive sign of acute myocardial ischemia and may persist beyond recovery of exercise-induced ischemia.

Methods
Regional LV transverse strain changes during the first one-third of diastole duration (strain imaging diastolic index [SI-DI]) were determined at baseline and 5 and 10 min after the exercise test in 162 patients with stable effort angina. The ratio of SI-DI before and after exercise (SI-DI ratio) was used to identify regional LV delayed relaxation.

Results
A total of 117 patients had significant (>50% of luminal diameter) coronary stenoses. The mean SI-DI decreased from 78.0 ± 9.7% to 27.6 ± 16.0% (p < 0.0001) in 191 territories perfused by coronary arteries with significant stenoses 5 min after the treadmill exercise, whereas it remained unchanged in 280 territories perfused by arteries with nonsignificant stenoses. Ten minutes after exercise, regional delayed relaxation was still observed in 85% of territories perfused by stenotic coronary arteries. An SI-DI ratio with a cutoff value of 0.74 had a sensitivity of 97% and a specificity of 93% to detect significant coronary stenosis in the receiver-operator characteristic curve.

Conclusions
Detection of post-ischemic regional LV delayed relaxation or diastolic stunning after treadmill exercise using SI is a sensitive and reliable method for the detection of coronary artery disease. (J Am Coll Cardiol 2009;53:698–705) © 2009 by the American College of Cardiology Foundation

Diastolic left ventricular (LV) abnormalities are sensitive early signs of myocardial ischemia and have the additional advantage of persisting longer than systolic disturbance (1–4). Ischemia-induced diastolic tardorelaxation or delay in the onset of regional relaxation has been shown in the perfusion territory of the involved coronary region in animal and clinical models (5–10). Quantitative analysis of prolonged regional LV diastolic dysfunction may provide a more sensitive estimation of the coronary region involved compared with detection of systolic dysfunction to detect differences between ischemic and nonischemic myocardium more accurately. Recently, we have shown that impaired or stunned regional diastolic function with delayed outward wall motion persisted beyond recovery after ischemia in patients with effort angina during the treadmill exercise stress test (11). Tissue Doppler imaging and derived strain and strain rate measurements have been proposed to better quantify regional myocardial deformation. However, these techniques depend on the Doppler angle and lack reproducibility (12). Strain imaging (SI) derived from 2-dimensional (2D) speckle-tracking echocardiography enables quantification of regional myocardial function without tethering effect and Doppler-angle dependency with high temporal resolution (13–15). The SI measures the extent of regional myocardial shortening and lengthening. Because of its high temporal and spatial resolution, SI may facilitate the application of novel quantitative parameters in ischemia detection. High-resolution tracking of regional myocardial activity by SI may provide a valuable and quantifiable means of detecting inducible ischemia with implications for stress echocardiography (16,17). The current study was designed...
to determine whether post-ischemic regional LV delayed relaxation or diastolic stunning occurring after treadmill exercise stress testing could be detected by using SI in patients with stable effort angina and coronary artery disease (CAD). If so, CAD could be diagnosed and stenotic coronary arteries could be identified noninvasively and accurately by the detection of post-ischemic regional LV delayed relaxation after treadmill exercise stress testing by using SI.

Methods

Patient population. One hundred sixty-seven consecutive patients who had Canadian Cardiovascular Society Classification II (18) stable effort angina and normal LV wall motion detected by standard echocardiography were recruited into this study. Consent was obtained to receive both treadmill exercise echocardiography including SI derived from 2D speckle tracking technology and coronary angiography. Patients with unstable angina, left main trunk disease, previous myocardial infarction, previous cardiac surgery, artificial pacemaker, nonsinus rhythm, significant valvular heart disease, chronic obstructive pulmonary disease, or congestive heart failure were not included. None had any apparent abnormalities in echocardiographic parameters including the LV end-diastolic diameter, fractional shortening, LV hypertrophy (wall thickness at end diastole >11 mm), or calculated LV mass index. Five patients were excluded from the analysis because of inadequate ultrasound images. The remaining 162 patients (ages 63 ± 10 years, 60% men) were studied. The study protocol was approved by the institutional ethics committee, and all patients gave written informed consent.

Exercise stress test and SI study. All patients underwent the treadmill exercise test with SI study within 1 week of coronary angiography. The SI was analyzed by an experienced echocardiography specialist who was blinded to the coronary angiography findings. Symptom-limited treadmill exercise stress testing was performed by using the standard Bruce protocol (19). Exercise was terminated in the presence of severe chest pain or other symptoms limiting further exercise, severe arrhythmia, ≥2 mm ST-segment elevation or depression, systolic blood pressure ≥250 mm Hg, diastolic blood pressure ≥130 mm Hg, or a decrease in systolic blood pressure ≥20 mm Hg. Heart rate, blood pressure, 12-lead electrocardiography, and symptoms at rest, during exercise, and for the first 10 min after exercise were recorded. Electrocardiographic findings during or after exercise were compared with those obtained at rest. The ST-segment depression ≥0.1 mV at 80 ms after the R-wave was considered to be significant for myocardial ischemia (20). If the chest pain persisted for 2 min or was too severe to be endured by the patient, sublingual nitroglycerin was administered. For the control group, 30 subjects (18 men and 12 women with a mean age of 57 ± 8 years) without chest pain or any cardiovascular disease who had had negative findings on treadmill exercise tests were also studied.

The SI study with the patients lying in the left lateral decubitus position was performed at baseline, and also 5 and 10 min after the treadmill exercise stress test. The SI was obtained by using a ultrasound system (Apio SSA-770A, Toshiba Medical Systems, Tokyo, Japan) with a 2.5-MHz phased-array transducer in the 3 standard LV apical views (apical 4-chamber, 2-chamber, and long-axis) and high frame rate (45 ± 5 frames/s). A novel software program was used to measure the transverse strain of myocardial segments. Two stable and well-defined consecutive cardiac cycles were acquired digitally for each view and stored on a magneto-optical disk for off-line analysis. Analysis of SI. Transverse strain images were obtained in each segment by using 2D speckle-tracking software (Toshiba Medical Systems). End-diastole and -systole were defined to occur at the R peak on the electrocardiographic trace and aortic valve closure on the 2D-mode profile, respectively. Cardiac cycles associated with atrial and/or ventricular extrasystolic beats, postextrasystolic cycle, or any other rhythm abnormalities were excluded. The end systolic values of strain at the closure of the aortic valve (A) and at the one-third point of diastole duration (B) were measured. The strain imaging diastolic index (SI-DI) was determined as (A − B)/A × 100% (Fig. 1) to assess the regional LV active relaxation (21,22). The ratio of SI-DI before and after exercise was defined as the SI-DI ratio and was used to identify regional LV delayed relaxation. Three major coronary perfusion territories were assigned as defined in the American Society of Echocardiography guidelines (23): 1) the mid-anteroseptal segment to the left anterior descending coronary artery; 2) the midanterolateral segment to the left circumflex branch; and 3) the mid-inferior segment to the right coronary artery. The mean SI-DI at baseline in 30 control subjects was 84 ± 7%, 86 ± 9%, and 85 ± 8% in the anteroseptal, anterolateral, and inferior segments, respectively. Interobserver variability for measurement of SI-DI was 7.2 ± 2.3% (n = 30), and intraobserver variability was 4.3 ± 1.5% (n = 30).

Quantitative coronary angiography. The coronary angiograms were analyzed by using the Cardiovascular Angiography Analysis System (CAAS II, PIE Medical Imaging, Maastricht, Limburg, the Netherlands) (24). End-diastolic frames were selected for edge-detection analysis, and the tip of the catheter was used as calibration. Reference diameter, minimal lumen diameter, and diameter stenosis were calculated. Significant coronary artery stenosis was considered present when ≥50% diameter stenosis of at least 1 major coronary artery was observed.

Statistical analysis. Values are presented as the mean ± standard deviation. Comparison of the SI-DI was performed with repeated measures of analysis of variance followed by the
Post-ischemic LV delayed relaxation after treadmill exercise. In 162 patients for whom data were analyzed, there were 486 potentially analyzed segments. Of these, 15 segments (3%) were excluded from SI analysis because of an uninterpretable signal. The heart rate was 77 ± 11 beats/min at 5 min after the treadmill exercise and 69 ± 10 beats/min at 10 min after the exercise. The systolic blood pressure was 149 ± 13 mm Hg at 5 min after the exercise and 137 ± 15 mm Hg at 10 min after the exercise.

Figures 2 and 3 show the changes of SI-DIs in the territories perfused by coronary arteries with significant and nonsignificant stenosis after treadmill exercise test.

Table 1 Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>162</th>
</tr>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>63 ± 10</td>
</tr>
<tr>
<td>Male/female</td>
<td>97/65</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.6 ± 0.2</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>67 ± 9</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>139 ± 11</td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>52 (32%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>92 (57%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>69 (43%)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>83 (51%)</td>
</tr>
<tr>
<td>Family history of heart disease</td>
<td>57 (35%)</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>123 (76%)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>86 (53%)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>83 (51%)</td>
</tr>
<tr>
<td>ACE inhibitors/ARB</td>
<td>70 (43%)</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>91 (56%)</td>
</tr>
<tr>
<td>Statins</td>
<td>62 (38%)</td>
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<tr>
<td>Echocardiographic characteristics</td>
<td></td>
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<tr>
<td>LVDd (mm)</td>
<td>46 ± 5</td>
</tr>
<tr>
<td>LVDs (mm)</td>
<td>27 ± 4</td>
</tr>
<tr>
<td>FS (%)</td>
<td>32 ± 6</td>
</tr>
<tr>
<td>IVSth (mm)</td>
<td>9 ± 1</td>
</tr>
<tr>
<td>LVPWth (mm)</td>
<td>9 ± 1</td>
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</tbody>
</table>

Values are presented as n (%) or mean ± SD.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BSA = body surface area; FS = fractional shortening of left ventricular long-axis diameter; HR = heart rate; IVSth = wall thickness of interventricular septum; LVDd = left ventricular diameter at end diastole; LVDs = left ventricular diameter at end systole; LVPWth = left ventricular posterior wall thickness; SBP = systolic blood pressure.
The mean SI-DI decreased from 78.0 ± 9.7% to 27.6 ± 16.0% (p < 0.0001) in 191 territories perfused by coronary arteries with a significant stenosis 5 min after the treadmill exercise stress test, whereas it remained essentially un-

Figure 2 Comparison of SI-DI Values at Baseline and 5 and 10 Min After Exercise

Comparisons of strain imaging diastolic index (SI-DI) values at baseline and 5 and 10 min after treadmill exercise in segments perfused by coronary arteries with significant (>50% of luminal diameter) stenosis. Changes in SI-DI were measured at (A) mid-anteroseptal (A-S), (B) mid-anterolateral (LAT), and (C) mid-inferior (INF) segments. The SI-DI significantly decreased 5 min after exercise as compared with that at baseline. Mean index was recovered but still depressed 10 min after exercise. All values are mean ± SD. *p < 0.0001.

Figure 3 Comparison of SI-DI Values at Baseline and 5 and 10 Min After Exercise

Comparisons of SI-DI values at baseline and 5 and 10 min after exercise in segments perfused by coronary arteries with nonsignificant (<50% of luminal diameter) stenosis. Changes in SI-DI were measured at (A) A-S, (B) LAT, and (C) INF segments. The SI-DI remained essentially unchanged after exercise as compared with that at baseline. All values are mean ± SD. p = NS. Abbreviations as in Figure 2.

changed from 82.0 ± 7.5% to 81.2 ± 11.5% (p = NS) in 280 territories perfused by normal coronary anatomy or <50% stenosis (Table 2). The SI-DI ratio was significantly decreased in territories perfused by stenotic arteries, but not in territories perfused by nonstenotic arteries (0.34 ± 0.18...
vs. 1.0 ± 0.15, p < 0.0001) 5 min after the treadmill exercise. Ten minutes after the treadmill exercise, regional delayed relaxation was still observed in 162 (85%) of 191 territories perfused by stenotic coronary arteries. The mean SI-DI increased to 34.6 ± 18.6% but was still significantly lower (p < 0.0001) than that at baseline. Receiver-operator characteristic analysis of SI-DI ratio at 5 min after treadmill exercise yielded optimal cutoff values of 0.74 for the detection of ≥50% coronary stenoses. Sensitivity and specificity of the SI-DI ratio were 97% and 93%, respectively. Similarly, the best cutoff value of the SI-DI ratio for the detection of ≥70% coronary stenosis was 0.39, which yielded a sensitivity and specificity of 97% and 88%, respectively (Fig. 4). An example of 2D speckle-tracking images and serial change of transverse strain curves from the study patients is shown in Figure 5.

**Discussion**

Post-ischemic regional LV delayed relaxation after exercise-induced myocardial ischemia. In the current study, regional LV delayed relaxation that probably developed during exercise was detected by the SI method both at 5 and 10 min after exercise-induced myocardial ischemia in patients with stable effort angina and CAD. Sensitivity and specificity for the prediction of ≥50% coronary stenosis were 97% and 93%, respectively. Underwood et al. (25) examined 79 studies with 8,964 patients using single-photon emission tomography in the diagnosis of CAD and found a sensitivity of 86% and specificity of 74%. With regard to stress echocardiography, Schuijf et al. (26) pooled 15 studies with 1,849 patients and found a weighted mean sensitivity and specificity of 84% and 82% for the detection of CAD, and a weighted mean sensitivity and specificity of 80% and 84% in 28 studies with 2,246 patients using dobutamine echocardiography. Our data suggest that detection of exercise-induced post-ischemic delayed relaxation using SI has the potential to improve the diagnostic accuracy of stress echocardiography for the detection of significant coronary disease. Techniques such as tissue Doppler-derived strain echocardiography and strain echocardiography that quantify regional mechanics are being increasingly investigated as a means of objectively identifying myocardial ischemia, and are able to distinguish ischemic from nonischemic segments (12,16,27). With conventional echocardiography, detection of ischemia is predicted on the demonstration of systolic abnormalities. However, diastole is an energy-dependent process (2,28), and ischemia-related diastolic abnormalities have been previously shown with several techniques. Visual wall motion analysis is unable to reliably assess diastolic events. Clinical studies have previously shown diastolic abnormalities using Doppler-derived strain echocardiography in CAD (29). However, the relationship of post-ischemic regional diastolic mechanical abnormalities to significant CAD in patients with effort angina has not been clearly elaborated. Knowledge of this relationship may allow the use of diastolic abnormalities to
detect CAD. Recently, we reported that regional delayed relaxation or tardorelaxation was observed after a treadmill exercise stress test in patients with stable effort angina and CAD, and this impairment persisted even 1 h after exercise, when normal regional systolic motion is completely restored (11).

**Regional myocardial changes in motion and deformation after acute ischemia.** Acute regional ischemia causes rapid, predictable, and reproducible change in deformation in a segment. The magnitude of these changes is proportional to the severity of the acute ischemic insult and is flow related (1,30). Systolic deformation decreases with increasing stenosis, whereas post-systolic thickening becomes more prominent. Reperfusion restores deformation to near normal, but some bulging and post-systolic thickening remain in the early phase as result of stunning (31). Jamal et al. (32) reported the typical sequence of changes in M-mode images of the at-risk wall after an acute coronary occlusion. Deformation and motion return to near normal after reperfusion (after a short initial period of hypercontractility caused by hyperemia). When myocardium is ischemic for a prolonged period and subsequently reperfused, deformation remains abnormal despite full restoration of perfusion (33). Monnet et al. (34) showed that, in stunned myocardium, deformation returns to normal within a period of 24 h of reperfusion and that this is paralleled by a decrease in post-systolic thickening.

The mechanisms underlying the phenomenon of ischemia-related post-ischemic deformation have been the subject of much debate. Three different explanations have been proposed, either delayed active contraction, late passive thickening, or elastic recoil overshoot after bulging. Türschner et al. (35) reported that with Thrombolysis In Myocardial Infarction flow grade 3 infarct reperfusion, end systolic wall thickness returned to baseline within 5 min whereas end diastolic wall thickness increased above baseline level after 1 min. Both wall thickness parameters then continued to increase logarithmically during the 60-min reperfusion period. Bragadeesh et al. (36) have reported that a major mechanism for post-ischemic regional LV dysfunction is myofibrillar edema, and as myofibrillar edema subsides with time, regional LV dysfunction improves.

**Study limitations.** The present study has several limitations with regard to application of the results to the clinical setting. First, it remains undetermined how long the regional delayed relaxation or stunning actually persists after the demand-ischemia. The duration of the observed diastolic stunning after the demand-ischemia is probably influenced by the total ischemic burden during the treadmill exercise testing and the severity of the coronary stenosis as well as endothelial function in the microvessels of the regional coronary circulation (11,17). Second, the success of this novel tracking algorithm depends on the quality of 2D echocardiographic images (13). Third, asynchronous LV relaxation may exist in patients with other cardiac diseases, such as idiopathic cardiomyopathy and hypertensive heart disease (37). A differential diagnosis may be required in these cases, although the abnormal regional LV relaxation may not be influenced by exercise in nonischemic heart disease as much as in cases with CAD. Fourth, in the present study, only the transverse strain component was assessed. Currently, transverse and longitudinal myocardial deformation can be analyzed in the apical view by using 2D speckle-tracking echocardiography (17), so it would be necessary to show that myocardial ischemia affects transverse and longitudinal function similarly. Thus, the effect of these factors on the relaxation index should be assessed in future studies before applying this method to differentiate patients with CAD from those without it.
Conclusions

Exercise-induced regional myocardial ischemia impairs regional diastolic wall motion in patients with CAD, and this impairment persists for 10 min after exercise. Echocardiographic evaluation of regional myocardial wall motion or delayed relaxation by SI is a useful noninvasive method for detection of prolonged post-ischemic diastolic dysfunction or stunning and for identification of the angina-provoking vessel. Detection of post-ischemic regional LV delayed relaxation after treadmill exercise using SI is a sensitive and reliable method for the diagnosis of CAD.

Reprint requests and correspondence: Dr. Katsuhisa Ishii, Department of Cardiology, Kansai Electric Power Hospital, 2-1-7 Fukushima, Fukushima-ku, Osaka 553-0003, Japan. E-mail: ishii.katsuhisa@b2.kepco.co.jp.

REFERENCES


Key Words: 2D speckle tracking echocardiography — post-ischemic delayed relaxation — diastolic stunning — exercise stress test — effort angina.