Abnormal Regional Left Ventricular Systolic and Diastolic Function in Patients With Coronary Artery Disease Undergoing Percutaneous Coronary Intervention

Clinical Significance of Post-Ischemic Diastolic Stunning

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Objectives
This study was designed to characterize both regional left ventricular (LV) systolic and diastolic function after percutaneous coronary intervention by using strain imaging (SI) derived from 2-dimensional speckle-tracking echocardiography.

Background
Ischemic insult after coronary occlusion affects not only regional LV systolic but also diastolic function.

Methods
Regional LV transverse peak strain and strain changes during the first one-third of diastole duration (strain imaging diastolic index [SI-DI]) were monitored in at-risk segments after percutaneous coronary intervention in 30 patients with coronary artery disease. The segments were divided into proximal and distal. Strain data in the at-risk segments were compared with values derived from remote nonischemic segments.

Results
Coronary occlusion induced a marked reduction in the systolic strain in both proximal and distal at-risk segments (from 36.9 ± 6.0% to 12.0 ± 3.9% and from 31.9 ± 5.6% to 6.2 ± 3.3%, respectively, p < 0.0001). Concomitantly, SI-DI values decreased (from 76.6 ± 5.3% to −21.2 ± 9.1% and from 72.5 ± 5.9% to −48.7 ± 20.8%, respectively, p < 0.0001). Upon reperfusion, systolic deformation parameters returned to near-normal pre-occlusion values. However, SI-DI values in the both proximal and distal at-risk segments decreased (43.2 ± 9.5%, p < 0.01, and −17.3 ± 11.1%, p < 0.0001, respectively) 30 min after reperfusion and were still lower (51.5 ± 9.9%, p < 0.01) in the distal at-risk segment 24 h after reperfusion.

Conclusions
SI analysis provides detailed mechanical characterization of regions with myocardial ischemic insult and can demonstrate post-ischemic diastolic stunning despite complete systolic functional recovery after reperfusion.

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could be detected by using SI in patients with stable effort angina and coronary artery disease.

**Methods**

**Patients.** We prospectively selected 35 consecutive patients with stable angina in whom elective PCI procedures were performed. Patients with either a history or electrocardiographic evidence of transmural myocardial infarction, previous coronary bypass grafting, a coronary collateral Rentrop classification (29) of 2 or 3, atrial or ventricular arrhythmia, pacemaker, bundle branch block, significant valvular heart disease, or congestive heart failure were excluded from the study. 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), and calculated LV mass index. After inclusion in the study, 2 patients were found to have a poor acoustic window, and ischemia-induced arrhythmias developed in 3 others. These 5 patients were not included in the subsequent data analysis. In the remaining 30 patients (51 to 73 years of age; mean age 61 ± 8 years, 6 female patients), the site of angioplasty was either the proximal site of the left anterior descending coronary artery (n = 12), left circumflex branch (n = 8), or right coronary artery (n = 10). The baseline clinical and cardiac characteristics of the 30 patients are listed in Table 1. After PCI, all patients received ticlopidine hydrochloride. All patients gave informed consent before participation in the study, which had been approved by our ethics committee.

**Coronary angiography and PCI.** All patients underwent standard left heart catheterization and coronary angiography via the radial or femoral approach. Coronary angiograms were obtained after the administration of intracoronary nitroglycerin just before and immediately after PCI. The coronary stenosis severity in the vessel to be monitored during angioplasty was assessed visually and was defined as >90% in all patients. No patient had evidence of an occluded coronary artery before the angioplasty procedure. In the study patients, multiple inflations (3 to 5 inflations) were performed. The angioplasty balloon was inflated for a period of 61 ± 4 s on the basis of the clinical evaluation and the decision was made in each case by the operating cardiologist. Immediately after the procedure, the angiographic control demonstrated a residual stenosis of <30% with TIMI (Thrombolysis In Myocardial Infarction) flow grade 3 in the dilated artery in all patients. The heart rate averaged 66 ± 9 beats/min before coronary angioplasty and did not change during balloon inflation (69 ± 10 beats/min, p = NS).

**Echocardiographic data acquisition.** All recordings were performed with the patients in the supine position on the catheterization table. Echocardiographic images were obtained by using an ultrasound system (Apio SSA-770A, Toshiba Medical Systems, Tokyo, Japan) with a 2.5-MHz phased array transducer in the apical long-axis or 2- or 4-chamber view and a high frame rate (45 ± 5 frames/s). A novel software program was used to measure 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 offline analysis. Three major coronary perfusion territories were assigned as defined in the American Society of Echocardiography guidelines (30). The mid-anteroseptal and apical anterior segments, imaged in the apical long-axis view, were considered proximal and distal at-risk segments, respectively, and the mid-inferolateral segment was considered the remote nonischemic segment during left anterior descending coronary artery PCI. The anterolateral mid and basal segments, imaged in the apical 4-chamber view, were considered proximal and distal at-risk segments, respectively, and the mid-inferoseptal segment was considered remote during left circumflex branch PCI. The inferior mid and basal segments imaged in the apical 2-chamber view were considered proximal and distal at-risk segments, respectively, and the mid-anterior segment was considered the remote nonischemic segment.

**Table 1 Baseline Clinical Characteristics**

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>61 ± 8</td>
</tr>
<tr>
<td>Male/female</td>
<td>24/6</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.7 ± 0.3</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>66 ± 9</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>135 ± 12</td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (30%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16 (53%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>13 (43%)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>11 (37%)</td>
</tr>
<tr>
<td>Family history of heart disease</td>
<td>10 (33%)</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>30 (100%)</td>
</tr>
<tr>
<td>Nitrate</td>
<td>18 (60%)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>16 (53%)</td>
</tr>
<tr>
<td>ACE inhibitors/ARB</td>
<td>8 (27%)</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>15 (50%)</td>
</tr>
<tr>
<td>Statins</td>
<td>22 (73%)</td>
</tr>
<tr>
<td>Echocardiographic characteristics</td>
<td></td>
</tr>
<tr>
<td>LVDd (mm)</td>
<td>47 ± 6</td>
</tr>
<tr>
<td>LVd (mm)</td>
<td>28 ± 6</td>
</tr>
<tr>
<td>FS (%)</td>
<td>33 ± 5</td>
</tr>
<tr>
<td>IVSth (mm)</td>
<td>9 ± 1</td>
</tr>
<tr>
<td>LVPWth (mm)</td>
<td>9 ± 1</td>
</tr>
</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; LVd = left ventricular diameter at end systole; LVPWth = left ventricular posterior wall thickness; SBP = systolic blood pressure.
Comparison of Analysis of SI. Transverse strain images were obtained in after balloon deflation. balloon inflation. Reperfusion data were recorded 2 and 30 min occlusion were collected 20 to 50 s after the onset of the first procedure. Data during coronary and remote nonischemic segment function were acquired immediately before the PCI procedures. Data during coronary occlusion were collected 20 to 50 s after the onset of the first balloon inflation. Reperfusion data were recorded 2 and 30 min after balloon deflation.

Analysis of SI. Transverse strain images were obtained in each segment by using 2D speckle-tracking software (Toshiba Medical Systems, Tokyo, Japan). End-diastole and -systole were defined as occurring at the R peak on the electrocardio-

graphic trace and aortic valve closure on the 2D-mode profile, respectively. Cardiac cycles associated with atrial and/or ventricular extrasystolic beats, post-extrasystolic cycle, or any other rhythm abnormalities were excluded. Peak strain ($\varepsilon_{\text{PEAK}}$) was defined as the highest strain value obtained for the transverse direction throughout the cardiac cycle. Time to peak strain (T$_e$) was defined as the interval from onset of the Q-wave to $\varepsilon_{\text{PEAK}}$ throughout the cardiac cycle. 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) value was determined as: (A – B)/A × 100% (Fig. 1) to assess the regional LV active relaxation (24,31,32) and was used to identify regional LV delayed relaxation. Because previous animal studies had shown a combination of a decrease in systolic deformation and an increase in post-systolic (early diastolic) deformation to be induced by acute ischemia (33), the following parameters were analyzed in each segment: $\varepsilon_{\text{PEAK}}$, T$_e$, and SI-DI values. The intraobserver and interobserver variability (in percentage of mean values) ranged from 7% to 10% for all strain parameters.

**Follow-up study.** Gray scale and SI follow-up data were collected for the all study patients 24 h after the PCI procedure. Regional strain parameters were analyzed for transverse function of at-risk segments in the left anterior descending artery, left circumflex branch, and right coronary artery and remote segments as well.

**Statistical analysis.** Values are presented as the mean ± SD. Comparison of $\varepsilon_{\text{PEAK}}$, T$_e$, and SI-DI values was performed with repeated-measures analysis of variance with Dunnett adjustment. Values of $p < 0.05$ were considered statistically significant.

### Results

**Regional function of the ischemic segments. BASELINE (PRE-OCCLUSION).** For each cardiac cycle, the transverse systolic thickening of each myocardial segment was characterized by positive strain values. During diastole, the myocardium thinned rapidly in early diastole, and strain values decreased, reaching the zero value at the end-diastolic reference point. The transverse $\varepsilon_{\text{PEAK}}$ was lower in distal...
at-risk segments compared with proximal at-risk segments (31.9 ± 5.6% vs. 36.9 ± 6.0%, respectively, p < 0.001) (Table 2).

**CORONARY OCCLUSION.** Balloon coronary occlusion induced considerable alternation in the segmental deformation of both the proximal and distal at-risk myocardium.
The transverse $e_{\text{PEAK}}$ in both at-risk segments was significantly reduced (12.0 ± 3.9% and 6.2 ± 3.3%, respectively), and myocardial bulging characterized by paradoxical mid-/late-systolic thinning in the transverse direction (negative systolic strain) was observed in 21 of 30 patients 50 s after coronary occlusion. Furthermore, $e_{\text{PEAK}}$ was significantly delayed in both at-risk segments, resulting in a prolonged $T_e$ during coronary occlusion compared with baseline data (Fig. 2, Table 2). Even 20 s after coronary occlusion, SI-DI values were significantly decreased compared with baseline in both the proximal and distal at-risk segments ($-21.2 \pm 9.1\%$ and $-48.7 \pm 20.8\%$, respectively) (Fig. 3, Table 3). All of these changes were consistently observed in the transverse direction for both proximal and distal at-risk segments and even more strikingly in distal at-risk segments.

**CORONARY REPERFUSION.** After 2 min of coronary reperfusion, the segmental transverse $e_{\text{PEAK}}$ in both the proximal and distal at-risk segments slightly overshoot the pre-occlusion values (42.0 ± 6.3% and 35.2 ± 6.0%, respectively) (Fig. 2, Table 2); however, SI-DI values in both the proximal and distal at-risk segments were significantly lower compared with baseline, even more strikingly in the distal at-risk segments ($-21.2 \pm 12.8\%$ and $-66.9 \pm 18.3\%$, respectively). After 30 min of coronary reperfusion, the mean SI-DI values increased in both the proximal and distal at-risk segments, but were still significantly lower than those at baseline (43.2 ± 9.5% and $-17.3 \pm 11.1\%$, respectively) (Fig. 3, Tables 2 and 3).

**Regional function of the remote nonischemic segments.** In the remote nonischemic segments, $e_{\text{PEAK}}$ increased (40.2 ± 5.2%, p < 0.0001) at the end of the balloon inflation and decreased (36.2 ± 5.7%, p < 0.01) 2 min after balloon deflation. However, SI-DI values did not change during PCI and after coronary reperfusion (Figs. 2 and 3, Tables 2 and 3).

**Follow-up analysis.** Analyzing the individual segmental response 24 h after successful PCI, the segmental transverse $e_{\text{PEAK}}$ in both the proximal and distal at-risk segments did not change compared with baseline. SI-DI values in the proximal at-risk segment returned to the pre-occlusion level (82.7 ± 5.5%, p = NS); however, 24 h after PCI, the SI-DI value in the distal at-risk segment was still significantly lower (51.5 ± 9.9%, p < 0.01) than that at baseline (Fig. 3, Table 3). Examples of 2D speckle-tracking images and serial changes of transverse strain curves during and after PCI from the study patients are shown in Figure 4.

**Discussion**

To our knowledge, this is the first study to directly assess regional systolic and regional diastolic function in areas with different degrees of myocardial ischemic insult during and after PCI by using 2D speckle-tracking imaging. Our results can be summarized as follows:
1. Segments with ischemia, either proximal or distal, have impaired systolic and diastolic regional function, expressed as reduced peak systolic strain and SI-DI values.

2. During ongoing ischemia, regional diastolic function is impaired more rapidly compared with regional systolic function.

3. Ischemic segments with preserved regional systolic contractility have persistent regional diastolic dysfunction 24 h after reperfusion.

**Changes in regional LV systolic function during acute ischemia.** The assessment of regional systolic function during acute ischemia by strain quantification has been extensively studied, in both animals (1,2,7,14,19) and patients (3–5). In the studies, systolic strain in segments with myocardial ischemia was reduced compared with findings for the remote segments, which is in accordance with our findings. In addition, our study demonstrates that distal at-risk segments have greater depression of $e_{\text{PEAK}}$ and prolongation of Te than proximal at-risk segments. In our study, risk region segments were subjected to reversible ischemic damage, and a transient overshoot of regional systolic function above pre-occlusion levels occurred with reperfusion. With brief coronary artery occlusion, this transient overshoot was characterized by increases in regional stroke work as well as the extent and velocity of shortening. The overshoot did not depend on adrenergic mechanisms and seemed to be related to reactive hyperemia (1,4). The Te was significantly longer in at-risk segments than in remote nonischemic areas. It is considered that these findings might be related to the phenomenon of post-systolic shortening (34).

**Post-ischemic regional LV delayed relaxation after reperfusion.** In this study, by using transverse strain measured by 2D speckle-tracking echocardiography, we were able to...
demonstrate that regions undergoing significant ischemic insult during coronary occlusion and reperfusion displayed persistent regional diastolic impairment. The at-risk segments exhibited only diastolic impairment, but not systolic dysfunction 24 h after reperfusion. Recently, we reported that regional delayed relaxation was observed after a treadmill exercise stress test in patients with stable effort angina and coronary artery disease when normal regional systolic motion is completely restored (24). Wijns et al. (2) reported that the diastolic component would have a lower ischemic injury threshold for its occurrence than would the systolic component, that is, the region that sustained less ischemic injury during coronary occlusion may develop prolonged isolated diastolic dysfunction despite restoration of coronary blood flow and recovery of regional systolic contractility. Moreover, Azevedo et al. (20) demonstrated the persistence of regional diastolic impairment in the distal at-risk segments for as long as 24 h after the transient ischemic episode after PCI by using 2D speckle-tracking imaging.

**Study limitations.** Our results should be transposed with caution to the clinical situations in which acute ischemia is potentially involved, and further investigation is required. First, this study was based on a limited number of observations made in a small population of patients, which would diminish the power of the drawn statistical inference. Second, the success of this novel tracking algorithm depends on the quality of 2D echocardiographic images (26). Third, the population studied included patients with comorbidities, such as hypertension and diabetes mellitus, which might influence the myocardial response to acute ischemia, although these aspects were not currently considered (35). Fourth, it remains undetermined how long the regional diastolic dysfunction or stunning actually persists after the supply ischemia. The duration of the observed diastolic stunning after the supply ischemia is probably influenced by the total ischemic burden during PCI and endothelial...
function in the microvessels of the regional coronary circulation (20). Okamura et al. (36) reported that the Doppler guidewire can detect a high-intensity transient signal immediately after balloon deflation during elective PCI. The microvascular obstruction may be one of the mechanisms of regional diastolic functional impairment. However, despite these limitations, these data consistently indicate a reduction in $e_{PEAK}$, prolongation of $T_e$, and post-ischemic diastolic stunning as hallmarks of the reaction pattern to transient myocardial ischemia in the transverse direction. **Clinical implications.** Our study suggests that the detection of regional wall motion abnormalities during diastole or delayed relaxation by 2D speckle-tracking imaging might uncover myocardial ischemia. The site of regional delayed relaxation coincided well with the area perfused by the angina-provoking vessel. Furthermore, the procedure is totally noninvasive, safe, and easy to perform and hence suitable for repetitive bedside monitoring of regional myocardial function during coronary revascularization or in an emergency department. Repeated use of this technique may allow the possibility of achieving complete differential diagnosis of chest pain syndrome in routine daily practice.

**Conclusions**

Using novel 2D speckle-tracking imaging, we have defined specific acutely ischemic changes within the at-risk segment for the transverse direction. We observed significant changes in regional deformation (reduction of $e_{PEAK}$ and prolongation of $T_e$) during acute ischemia. Importantly, this study demonstrates that reversibly ischemic regions can present with persistent regional diastolic dysfunction despite complete recovery of regional systolic contractility after perfusion has been restored, and regional diastolic function can be quantified in detail by using strain analysis with 2D speckle-tracking imaging.

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Key Words: 2-dimensional speckle-tracking echocardiography • coronary artery disease • percutaneous coronary intervention • postsystolic diastolic stunning • strain.