Impaired Subendocardial Wall Thickening and Post-Systolic Shortening Are Signs of Critical Myocardial Ischemia in Patients With Flow-Limiting Coronary Stenosis

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Background: The early diagnosis of myocardial ischemia is still challenging. The aim of the present study was to determine whether subendocardial hypokinesis and post-systolic contraction could be early markers of myocardial ischemia.

Methods and Results: Thirty-one consecutive patients with flow-limiting severe coronary stenosis but without visually abnormal left ventricular wall motion underwent quantitative echocardiography. Myocardial strain was measured using layer-by-layer analysis in severely hypoperfused segments. Radial strain (RS) was measured in the subendocardial, subepicardial, and total wall (innerRS, outerRS, and totalRS, respectively). Circumferential strain (CS) was also measured as 3 separate layers: subendocardial, mid-layer, and subepicardial layers (innerCS, midCS, and outerCS, respectively). Post-systolic shortening (PSS) was defined as the peak strain after end systole, and post-systolic strain index (PSI) was calculated as PSS divided by end-systolic strain. TotalRS was similar between ischemic and normally perfused segments, but innerRS and inner/outer RS ratio were significantly smaller in the ischemic segments than in corresponding segments in healthy subjects. Receiver operating characteristic analysis identified an optimum cut-off for PSI of 0.6. The combined criteria of inner/outer RS ratio <1.0 and PSI >0.6 achieved 95% specificity for the presence of flow-limiting stenosis.

Conclusions: Combined assessment of both subendocardial contractile impairment and PSS is very useful in identifying a severely hypoperfused left ventricular wall even without visual wall motion abnormality. (Circ J 2011; 75: 1934–1941)

Key Words: Ischemic heart disease; Post-systolic shortening; Transmural strain heterogeneity
Figure 1. (A) Total, (B) inner, and (C) outer radial strain (RS) curves of a representative mid anteroseptal wall in a normal subject. The black dashed line indicating end systole, at which the left ventricular area becomes smallest during the cardiac cycle, was derived automatically by software. White arrowheads, peak systolic RS. In this case, peak systolic strain was the same as end-systolic strain. Black arrowheads, post-systolic strain. In this subject, peak systolic total RS was 42%, inner strain 49%, outer strain 35%, and inner/outer strain ratio was calculated as 1.4.
In the present study, to assess the diagnostic impact of strain measurement using 2D-STI on the detection of myocardial ischemia, we investigated subendocardial strain and PSS quantitatively in patients with flow-limiting coronary stenosis but visually normal LV wall motion.

**Methods**

**Patient Characteristics**

Of 212 patients with coronary artery disease confirmed on coronary angiography from April 2007 to February 2008, 92 patients (23%) had a 99% stenosis with delayed flow or 100% occlusion with poor collateral flow in the left anterior descending coronary artery. Among these, 34% of patients had normal wall motion according to visual assessment on echocardiography. We studied those patients with visually normal wall motion but with 99% stenosis with delay or 100% occlusion with poor collateral flow in the left anterior descending coronary artery. Patients with the following were excluded: abnormal Q wave on 12-lead electrocardiogram, abnormal laboratory data indicating myocardial infarction, rhythm other than normal sinus rhythm, significant valvular heart disease, and insufficient echocardiographic image quality for analysis. Informed consent was obtained from all patients after a detailed explanation of the study was provided. For normal controls, corresponding wall segments were studied in 52 patients who complained of chest pain but who had no significant stenosis or coronary spasm on coronary angiography.

**Echocardiography**

The echocardiographic image was analyzed to evaluate LV strain with 2-D speckle tracking software (2D Wall Motion Tracking, Toshiba Medical Systems, Tochigi, Japan). A Toshiba ARTIDATM ultrasound system (Toshiba Medical Systems) equipped with a multifrequency transducer was used to perform 2-D echocardiography, which was obtained with the patients lying in a supine or slightly left lateral decubitus position. The frame rate for 2-D echo was 46 ± 6 frames per second. After obtaining LV short-axis images, we analyzed anterior and anteroseptal segments as left anterior descending artery territory, inferior and inferoseptal segments as right coronary artery territory, and lateral and inferolateral segments as left circumflex coronary artery territory. The endocardial border on the short-axis image at end systole was traced manually, followed by manual tracing of the epicardial border; thereafter, the software automatically created a midwall tracking line at the center between these 2 borders. The 2D-STI software uses the sum of squared differences method to find the most similar speckle pattern in subsequent frames. We measured peak and end-systolic radial and circumferential strain (RS) and CS (Figure 1). Radial strain (RS) was defined as the percentage change in wall thickness in the direction perpendicular to the endocardium and away from the LV lumen, and CS was defined as the percentage change in regional length in the circumferential direction. Three types of RS were measured: total, inner-half, and outer-half RS (totalRS, innerRS, outerRS, respectively), and the inner/outer RS ratio was calculated. Three types of CS were also mea-
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Measured: inner, mid-layer, and outer CS (innerCS, midCS, outerCS, respectively), and the inner/mid CS ratio was calculated. PSS was defined as the peak strain after end systole. The peak of the strain curve was defined if the strain rate curve passed through zero (Figure 2). End systole was defined as the time at which the LV short-axis chamber area reached a minimum. When post-systolic strain was present, the post-systolic strain index (PSI) was calculated as the post-systolic strain/end-systolic strain ratio.

Reproducibility
Fifteen studies were selected at random for the assessment of intra- and inter-observer reproducibility of innerCS, midCS, and outerCS, and innerRS, outerRS, and totalRS measurements. To test intra-observer variability, a single observer analyzed the data twice at intervals of more than 1 week. To test inter-observer variability, a second observer analyzed the data without knowledge of the first observer’s measurements. Reproducibility was assessed as the mean percent error (absolute difference divided by the mean of the 2 individual observations).
**Statistical Analysis**

Results are expressed as number or mean±SD. Baseline characteristics and echocardiography data at rest were analyzed using Student’s t-test for continuous variables and with chi-square and Fisher’s exact tests for categorical variables. One-way analysis of variance and Fisher’s post-hoc analysis were used for comparison between repeated measurements. Receiver operating characteristic (ROC) curve analysis and comparison of ROC curves between parameters were carried out. Differences were considered significant for P<0.05. Statistical calculations were carried out using Dr SPSS II for Windows (SPSS, Chicago, IL, USA).

**Results**

A total of 31 patients with flow-limiting left anterior descending coronary arterial stenosis but without visually apparent regional wall motion abnormalities (27 men, 4 women, age: 65±9 years) and 52 normal, healthy subjects were enrolled in the present study. Patient characteristics are given in Table 1. There were no significant differences in demographic and routine echocardiographic characteristics between the 2 groups. Among 64 LV wall segments showing severe ischemia, 9 segments (14%) were excluded from the strain analysis due to insufficient quality of speckle tracking.
Strain and Strain Gradient
In regard to peak systolic RS, although totalRS was similar in ischemic segments and normal control segments, innerRS was smaller and outerRS was larger than those in the normal group (Figure 3A). In the normal group, innerRS was greater than outerRS and mean inner/outer RS ratio was >1 (1.7±0.9), whereas in the ischemic segments, innerRS was smaller than outerRS, and as a result, mean inner/outer RS ratio was <1 (0.8±0.7; Figure 3B). For peak systolic CS, innerCS was smaller and mid-CS was larger in ischemic segments than in normal group segments (Figure 3C). Therefore, inner/mid CS ratio was smaller in segments with ischemia than in normal group segments (Figure 3D). ROC curve analysis showed that the area under the curve (AUC) was statistically significantly >0.5 for inner/outer RS ratio (AUC, 0.85; P<0.001), innerCS (AUC, 0.78; P<0.001), outerRS (AUC, 0.71; P<0.001; Figure 4A), inner/mid CS ratio (AUC, 0.73; P=0.002), and midCS (AUC, 0.69; P=0.002; Figure 4B).

PSS and PSI
Visual recognition of PSS was achieved in 81% of the ischemic and in 48% of the normal segments (P=0.023). On ROC curve analysis, AUC were statistically significantly >0.5 for midCS PSI (AUC, 0.70; P=0.042) and outerCS PSI (AUC, 0.75; P=0.010; Figures 4C, D).

Strain Gradient and PSI
When the cut-off for the inner/outer RS ratio was set at <1.0, sensitivity and specificity for the presence of flow-limiting coronary stenosis were 0.73 and 0.88, respectively (Table 2). If there was no PSS or if midCS PSI was <0.60, sensitivity was 0.73 and specificity was 0.77 for the absence of flow-limiting coronary stenosis. In addition, the combined criteria of inner/outer RS ratio <1.0 and PSI >0.60 achieved 95% specificity for the presence of flow-limiting coronary stenosis, and the combination of inner/outer RS ratio >1.0 or PSI >0.60 achieved 90% sensitivity for the presence of flow-limiting coronary stenosis.

Reproducibility
Intra- and inter-observer variability were as follows: totalRS, 9.0±5.5% and 16.2±6.7%; innerRS, 11.2±4.1% and 19.9±8.7%; outerRS, 11.3±5.5% and 18.6±9.9%; innerCS, 5.3±2.5% and 9.2±4.8%; midCS, 7.0±3.6% and 20.3±6.9%; and outerCS, 9.7±3.0% and 11.7±4.0%; respectively.

Discussion
In the present study, only patients with a severe stenotic lesion in the left anterior descending artery were selected, and we analyzed layer-by-layer strain characteristics of LV wall segments showing subtle ischemia using 2D-STI echocardiography. In patients with flow-limiting coronary stenosis but without impaired contraction based on visual judgment, wall thickening was decreased in the subendocardium. Furthermore, significant midwall circumferential PSS was observed in ischemic segments. These results showed that with 2D-STI, we could quantify the transmural strain gradient and abnormal strain time course and identify early ischemia of the left ventricle.

Transmural Heterogeneity of Myocardial Contraction
Several ultrasonic crystal-derived experimental and clinical studies using tissue Doppler echocardiography have confirmed transmural heterogeneous strain distribution in the myocardium. In the normal left ventricle, greater myocardial wall stress and strain occur in the subendocardium rather than in the subepicardium. In the present study, 2D-STI of transmural strain distribution demonstrated that normal segments had greater RS and CS in the subendocardial layer than in the subepicardial layer, which is consistent with the results of previous studies.

Subendocardial Dysfunction During Ischemia
Experimental studies have shown that if the reduction of epicardial coronary blood flow is mild, overall wall thickening abnormality is not apparent. When further reduction of blood flow occurs, overall wall thickening abnormality develops progressively. In the present study, subendocardial wall thickening had deteriorated even when the overall wall thickening abnormality was not significant. Kuwada and Takenaka previously demonstrated a similar phenomenon using color M-mode tissue Doppler tracking in clinical chronic ischemia. Therefore, quantitative analysis of subendocardial systolic mechanics may be more sensitive than the objective assessment of total wall thickening for the detection of early ischemia.

Mid-Wall and Epicardial Strain Augmentation in Hypoperfused Segments Without Obvious Wall Motion Abnormality
In the present study, outerRS and midCS in hypoperfused but normal wall motion segments were greater than that in the corresponding normal segment. This suggests the presence of mid-wall and epicardial enhanced strain that compensates for the subendocardial dysfunction. Preserved totalRS has also been previously reported by Chan et al in patients with subendocardial infarction confirmed on late gadolinium-enhanced magnetic resonance imaging. They discussed the mechanism and also indicated that epicardial augmentation of wall thickening occurs in subendocardial necrosis. From the point of view of myocardial metabolism, although wavefront necrosis starts from the subendocardium in epicardial coronary stenosis, increased production of high-energy phosphates in the subepicardium to compensate for the reduction in high-energy phosphate production in the subendocardium has been reported. Furthermore, in the hypertensive heart, subepicardial compensatory hypertrophy, an attempt to reduce subendocardial wall stress to preserve the ejection fraction of the left ventricle, has been reported. All of these findings support the concept that vertical compensatory enhanced action is possible.

PSS
PSS rather than systolic wall thickening abnormality has been proposed as the upstream site in the ischemic cascade in experimental and clinical studies of acute flow-limiting coronary stenosis. Furthermore, PSS has been reported to be a

| Table 2. Sensitivity and Specificity to Detect Severe Flow-Limiting Stenosis |
|-----------------|---------|-------|
| Inner/outer RS ratio <1.0 | Sensitivity (%) | Specificity (%) |
| MidCS PSI >0.6 | 73 | 88 |
| Inner/outer RS ratio <1.0 or PSI >0.6 | 90 | 73 |
| Inner/outer RS ratio <1.0 and PSI >0.6 | 36 | 95 |

RS, radial strain; CS, circumferential strain; PSI, post-systolic strain index.
sensitive marker of ischemia induced by dobutamine stress,\textsuperscript{30} and has been observed in segments at rest without concomitant ischemia in coronary artery disease patients.\textsuperscript{31,32} The presence of PSS itself, however, is not a specific sign of ischemia, especially in the subepicardium,\textsuperscript{33,34} and more than one-third of normal LV segments had PSS on longitudinal strain measurements.\textsuperscript{34} PSS has been detected in conditions other than coronary artery disease such as LV hypertrophy and volume overload.\textsuperscript{15,34} Higher-magnitude PSI (>60\%) was thought to indicate pathologic PSS in the present study. These findings are comparable with those of previous experimental and clinical studies.\textsuperscript{19,34} Furthermore, using subendocardial 2D-STI, the presence of subendocardial contractile deterioration can be used to separate ischemic from non-ischemic PSS, and the combination of these 2 parameters (impaired subendocardial thickening and post-systolic circumferential shortening) may be the best of the quantitative findings available for identifying ischemia at rest.

**Study Limitations**

There were several limitations to the present study. First, we did not measure longitudinal strain\textsuperscript{35} and its gradient. No apparent transmural gradient, however, has been reported to date in the longitudinal direction of the left ventricle.\textsuperscript{3} This may be due to the orientation of the fibers in the left ventricle.

Second, there was poor inter-observer reproducibility in RS and midCS measurements. Calculation of innerRS, outerRS, and midCS requires intramural speckle tracking. Tracking of mid-wall echo speckle is challenging because of the hazy speckle pattern produced in comparison to the strong echo from the myocardial contour.\textsuperscript{11} Speckle is an inherent characteristic of ultrasound imaging, and it arises because sub-resolution scatter causes interference patterns in the image.\textsuperscript{35} Therefore, the observed speckle pattern does not correspond to the underlying structure of the tissue. As the tissue is deformed, the relative phases of each scatter echo vary, and a new speckle pattern is formed. The speckle pattern will, however, gradually change as the structure is deformed. As long as these changes are small, the local motion of material points between 2 frames can be estimated by tracking of the speckle patterns in the images.\textsuperscript{36} In an open-chest animal model, intramural speckle tracking-derived strain was found to correspond with the ultrasonic crystal to the same degree as the strain derived from speckle tracking of the myocardial border.\textsuperscript{11} Another source of measurement error for RS may be due to the small denominator in the definition of RS:

\[
\text{strain} = \frac{(L_f - L_i)}{L_i},
\]

where \( L_i \) is the initial length at diastole. For innerRS, \( L_i \) is around 4 mm in normal left ventricle. In this case, RS of 20\% means an increase of only 0.8 mm in systolic wall thickness. In addition, systolic whole heart movement to the apex and endocardial complex surface structure might affect wall thickness measurements and result in substantial error in RS. Such poor reproducibility should be overcome by further improvements in speckle tracking technique and 3-D tracking in echocardiography.

Third, the present study was based on off-line retrospective analysis of the echocardiogram. A prospective blinded study to demonstrate the accuracy of the strain parameters should be conducted to establish the clinical utility of this method.

Fourth, other than the existence of non-specific ST-T changes in the electrocardiogram, no other objective confirmation of resting myocardial ischemia was provided in the subjects. Previous investigation using a coronary ligation animal model, however, suggested the presence of myocardial ischemia at rest in situations of severe flow-limiting coronary stenosis.\textsuperscript{37}

**Clinical Implications**

The early non-invasive diagnosis of ischemic myocardium has both important therapeutic and prognostic implications. Typical chest pain and echocardiographic evidence of myocardial ischemia, however, occur only in a limited number of patients with established myocardial ischemia.\textsuperscript{38} It is well known that in the temporal sequence of the ischemic cascade, regional wall motion abnormality can appear earlier than do electrocardiogram changes or chest pain,\textsuperscript{39,40} and the conventional echocardiographic assessment of wall motion often fails to identify ischemia. The present study found that reduced subendocardial wall thickening accompanying apparent PSS at rest may be a useful marker for the identification of severe flow-limiting stenosis. In such patients, early invasive diagnosis followed by immediate revascularization may help to prevent myocardial necrosis. If preserved subendocardial wall thickening and absence of apparent PSS are identified, this should indicate normal coronary circulation with a specificity of 95\%. In such patients, the probability of the presence of flow-limiting coronary stenosis may be low, and an urgent diagnostic procedure would not be required. Therefore, the use of multi-layer strain echocardiography to detect concealed subendocardial contractile abnormalities and PSS might exclude patients from unnecessary emergent coronary intervention. This new method might contribute to appropriate clinical decision making.

**Conclusions**

The present results indicate that the combination of impaired subendocardial thickening and post-systolic circumferential shortening are clinically useful measurements even in LV wall segments in which deterioration of contraction cannot be identified visually. Quantitative analysis using layer-by-layer echo speckle tracking imaging was superior to conventional visual assessment of myocardial contractility in the evaluation of clinically severe myocardial ischemia.

**Disclosure**

No forms of financial support were received for this study, and no author has an association with industry that would pose a real or perceived conflict of interest.

**References**


