Follow-up of Patients after Coronary Intervention by Non-stress Echocardiography

—Detection of $\geq 75\%$ Coronary Artery Stenosis with Strain Rate Function—

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\section*{ABSTRACT}

\textbf{Background} : In combination with coronary angiography (CAG), stress echocardiography is the one of the screening methods to detect coronary artery stenosis after percutaneous coronary intervention (PCI), although a non-stress method is desirable from the standpoint of patients burden and time-consuming at out-patient clinic. Toward that end, the potential of non-stress echocardiography with strain rate (SR) analysis was examined.

\textbf{Method} : The apical views of the left ventricular wall motion were evaluated by longitudinal two-dimensional (2D) SR to yield four parameters: 100\textsuperscript{-} and 200\textsuperscript{-}msec SR values, and minimum SR values between 100\textsuperscript{-} to 200\textsuperscript{-}msec and mean SR values during 100\textsuperscript{-} to 200\textsuperscript{-}msec. Diagnostic accuracy with these parameters for coronary artery stenosis was assessed by determining the coefficients of discriminant function that best predicts an independent diagnosis.

\textbf{Results} : The following discriminant function yields 86.39\% probability of diagnosis of ≥75\% stenosis of coronary artery when discriminant score $Z>0: Z = 4.91 + 1.02 \times (100\textsuperscript{-}msec \text{ SR value}) + 1.23 \times (200\textsuperscript{-}msec \text{ SR value}) - 0.46 \times \text{(minimum \text{ SR value})} + 4.83 \times \text{(mean \text{ SR value})}$.

\textbf{Conclusion} : Thus, 2D SR analysis of resting apical views with discriminant function is as diagnostically accurate for coronary artery stenosis as stress echocardiography. By non-stress echocardiography in combination with CAG, it is possible enough to follow-up patients more frequently and precisely after PCI.

\textbf{Key words} : Follow-up of post-coronary intervention patients, Strain rate discriminant function of non-stressed echocardiography, Combination method of strain rate function and coronary angiography

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INTRODUCTION

Increasing prevalence of coronary artery disease and percutaneous coronary intervention (PCI) has intensified the significance of early detection of restenosis or progression of new lesions, thus emphasizing the need for periodical screening of coronary artery stenosis (CAS) after PCI by some methods beside CAG. Treadmill (exercise) electrocardiography (ECG) is the primary diagnostic modality, although stress echocardiography with inotropic drugs is also used. Exercise ECG is convenient. However, its diagnostic accuracy depends on lesions from 60% to 100%\(^1\sim^3\). So it cannot be said that it is a screening test reliable enough after PCI. With dobutamine stress echocardiography, variable rates for sensitivity, specificity, and diagnostic accuracy have been reported in the literature\(^4\sim^11\). Although these rates are better than those with exercise ECG, dobutamine stress echocardiography is inconvenient, due to the necessity of a physician to handle it by himself or at least to supervise it. From the standpoint of patient burden of palpitation at dobutamine peak dose, we hesitate to do this test frequently. In addition, it is time-consuming than ordinary screening echocardiography. Convenient, non-invasive and easy-doing screening test which can be done at out-patient clinic or even at cardiologists’ office without physician’s attendance and have satisfactory accuracy for CAS is therefore required in daily clinical practice. With this objective, we examined whether CAS can be detected by two-dimensional (2D) resting echocardiography. We also analyzed resting left ventricular (LV) wall motion by the 2D strain rate (SR) method, which has no angular dependence, thereby differing from one-dimensional tissue-velocity imaging (TVI) using Doppler sonography\(^12\).

METHODS

1 Study population

Among 548 patients who underwent CAG between June 1, 2003 and June 30, 2006 because of suspected CAS by dobutamine stress echocardiography, non-stress echocardiograms of total 179 patients were retrospectively analyzed in order to know whether non-stress echocardiography is reliable enough to detect CAS or not. They consisted of 108 patients who had normal coronary arteries and 71 patients who had significant (≥75% stenosis) single vessel coronary artery disease. These two groups were enrolled in the study (Table 1). Being afraid that myocardial ischemic change of patients with multi-vessel disease may be overestimated as it is probably affected by the nearest stenotic coronary artery, patients with multi-vessel coronary artery disease were not enrolled in the study. Patients with any other kinds of heart disease, including old myocardial infarction are not included.

The study was approved by the clinic’s ethics committee, and informed consent was obtained from all enrolling patients.

2 Echocardiographical images

Images were recorded by the tissue octave method using a cardiac ultrasound diagnostic device, Vivid 7 Dimension digital ultrasound system, Version 4.1.1 (General Electric, Inc., U.S.A.), and 1.5/4.0 MHz active-matrix array (AMA) probe. Resting LV wall motion in the recorded images was analyzed by longitudinal 2D SR analysis using off-line EchoPAC PC Version 4.1.1. Each patient’s endocardium was manually traced using EchoPAC PC analysis system in each of the three planes in apical views in order to set acceptable regions of interest (ROIs) in 18 segments. “Acceptable” means that
Table 1: Classification of patients with normal and single-vessel coronary artery disease

<table>
<thead>
<tr>
<th></th>
<th>LAD</th>
<th>RCA</th>
<th>LCX</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 75% stenosis</td>
<td>26 (As)</td>
<td>24 (Bs)</td>
<td>21 (Cs)</td>
<td>71 patients</td>
</tr>
<tr>
<td>Normal CAG</td>
<td>38 (An)</td>
<td>36 (Bn)</td>
<td>34 (Cn)</td>
<td>108 patients</td>
</tr>
<tr>
<td>Total</td>
<td>64</td>
<td>60</td>
<td>55</td>
<td>179 patients</td>
</tr>
</tbody>
</table>

LAD: left anterior descending coronary artery, RCA: right coronary artery, LCX: left circumflex coronary artery. Patients with 99% stenosis or total occlusion are not included in this study.

**Fig. 1** The SR curves of the 6 sample points
The upper left of the screen shows the ROI with color display, and the sample points are automatically indicated with 6 colors at the center of each of the 6 segments per view.

the central line of ROIs is moving with the underlying LV wall simultaneously and each segment of ROIs has enough myocardial tissue data to be tracked\(^{(10)}\). So “Acceptable” means “Analyzable successfully". The eighteen acceptable ROIs were successfully set and ROIs were manually adjusted to scale to the narrowest width visible on the monitor, which was about 1/4 of the full thickness of the LV wall since myocardial ischemia started from the subendocardial area. A total of 18 segments were assessed in the three planes, and the SR curve of the centroid of each segment was automatically measured (Fig. 1). The central region of the anterior wall of the apical two-chamber (Ap-2ch) view was considered as the left anterior descending (LAD) coronary artery bed, the central region of the inferior wall in the same view was considered the right coronary artery (RCA) bed, and the central region...
Table 2 Patient numbers of normal and stenosis groups in three coronary areas included in the preliminary study

<table>
<thead>
<tr>
<th></th>
<th>LAD</th>
<th>RCA</th>
<th>LCX</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥75% stenosis</td>
<td>11</td>
<td>10</td>
<td>12</td>
<td>33 patients</td>
</tr>
<tr>
<td>Normal CAG</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>30 patients</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>20</td>
<td>22</td>
<td>63 patients</td>
</tr>
</tbody>
</table>

as: patients with ≥75% stenosis of the LAD, an: patients with normal LAD,
bs: patients with ≥75% stenosis of the RCA, bn: patients with normal RCA,
cs: patients with ≥75% stenosis of the LCX, cn: patients with normal LCX.

Patients with 99% stenosis or total occlusion are not included in this study.

of the posterior wall of the long-axis apical (Ap-LAX) view was considered as the left circumflex coronary artery (LCX) bed.

3 Preliminary study

Prior to this study, a preliminary study was conducted with a limited number of patients in order to examine the features of longitudinal 2D SR curves (Table 2, Fig. 2). The mean values obtained during systole were substantially different between normal patients and those with coronary artery disease. Minimum values were also different for patients with LAD and LCX stenoses, but not for those with RCA stenosis. The time to minimum values did not differ, falling between 100- to 200-msec in most patients, regardless of the disease status and heart rate. This suggested that the times to minimum value fell within the 100- to 200-msec interval that approximately corresponds to the mid-systolic phase, despite the fact that the mean and minimum SR values are elevated in patients with coronary artery disease. Besides these advantageous features, the comparison of SR pattern during this interval can also be considered representative of the entire curve. Considering this, we chose the four parameters described above (100-msec SR, 200-msec SR, minimum SR between 100- to 200-msec and mean SR during 100- to 200-msec) for this study (Fig. 3).

4 Statistical analysis

These four values were compared between the following group pairs: stenotic-LAD (As) and normal-LAD (An), stenotic-RCA (Bs) and normal-RCA (Bn), and stenotic-LCX (Cs) and normal-LCX (Cn). Results were summarized in terms of mean and standard deviation (SD). Unpaired t-test was used to compare groups, and statistical significance was declared at p<0.05.

RESULTS

All four parameters had satisfactory sensitivity, specificity and accuracy for the three coronary arteries (Table 3). All four parameters were statistically and significantly different between the groups in the LAD (p<0.001), RCA (p<0.001), and LCX (p<0.001) group pairs. In each group pair, the stenotic-artery group showed higher means for each of the four parameters, i.e., all four SR parameters in the CAS groups (As, Bs, and Cs) were significantly higher than in the corresponding normal groups (An, Bn, and Cn) (Fig. 4).

A discriminant analysis with the parameters was performed. The discriminant probability was
Fig. 2 Results of the preliminary study
SR values are summarized as mean±SD. Systolic mean: the mean SR values of the entire systolic period. Systolic minimum: the minimum SR values of the entire systolic period. Time to systolic minimum: Time to the minimum SR value. Time to the minimum SR value was between 100 msec and 200 msec in most of the normal patients and stenosis patients.

85.06% ($p<0.001$) for two parameters (100- and 200-msec SR values). Adding the minimum SR value increased the discriminant probability only slightly (85.28%, $p<0.001$). The discriminant probability was 86.39% for all four parameters ($p<0.001$), indicating that the mean parameter is the most useful
Fig. 3  Four parameters used for the analysis during contraction period
1: the 100 msec SR value, 2: the 200 msec SR value, 3: the minimum SR value between 100 msec and 200 msec, 4: the mean SR value during 100 msec and 200 msec

Table 3  Sensitivity, specificity and accuracy of the 4 parameters for each of the 3 coronary arteries

<table>
<thead>
<tr>
<th></th>
<th>out−off val (1/s)</th>
<th>sn (%)</th>
<th>sp (%)</th>
<th>ac (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LAD ≥75% stenosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 ms. SR</td>
<td>−0.67</td>
<td>88.46</td>
<td>89.47</td>
<td>89.06</td>
</tr>
<tr>
<td>200 ms. SR</td>
<td>−0.71</td>
<td>96.20</td>
<td>81.58</td>
<td>87.50</td>
</tr>
<tr>
<td>100~200 ms. SR min.</td>
<td>−0.96</td>
<td>92.31</td>
<td>92.11</td>
<td>92.19</td>
</tr>
<tr>
<td>100~200 ms. SR mean</td>
<td>−0.70</td>
<td>92.31</td>
<td>92.11</td>
<td>92.19</td>
</tr>
<tr>
<td><strong>RCA ≥75% stenosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 msec. SR</td>
<td>−0.72</td>
<td>83.33</td>
<td>94.44</td>
<td>90.00</td>
</tr>
<tr>
<td>200 msec. SR</td>
<td>−0.93</td>
<td>83.33</td>
<td>75.00</td>
<td>78.33</td>
</tr>
<tr>
<td>100~200 ms. SR min.</td>
<td>−1.17</td>
<td>79.17</td>
<td>86.11</td>
<td>83.33</td>
</tr>
<tr>
<td>100~200 ms. SR mean</td>
<td>−0.84</td>
<td>87.50</td>
<td>88.89</td>
<td>88.33</td>
</tr>
<tr>
<td><strong>LCX ≥75% stenosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 ms. SR</td>
<td>−0.82</td>
<td>76.19</td>
<td>70.59</td>
<td>72.72</td>
</tr>
<tr>
<td>200 ms. SR</td>
<td>−0.74</td>
<td>80.95</td>
<td>85.29</td>
<td>83.64</td>
</tr>
<tr>
<td>100~200 ms. SR min.</td>
<td>−1.10</td>
<td>85.71</td>
<td>88.23</td>
<td>87.27</td>
</tr>
<tr>
<td>100~200 ms. SR mean</td>
<td>−0.69</td>
<td>85.71</td>
<td>97.06</td>
<td>92.73</td>
</tr>
</tbody>
</table>

sn: sensitivity, sp: specificity, ac: accuracy, SR: strain rate, min.: minimum value, mean: mean value

among them. For all four parameters, the following discriminant function equation was obtained for diagnosis of ≥75% stenosis when a discriminant score (Z) is greater than zero: \( Z = 4.91 + 1.02 \times (100\text{-msec SR value}) + 1.23 \times (200\text{-msec SR value}) - 0.46 \times (\text{minimum SR value}) + 4.83 \times (\text{mean SR value}) \).
**Fig. 4 Mean±SD of four parameters of 3 areas**

In all areas of the three coronary arteries (LAD, RCA, and LCX), 4 parameters showed significant differences ($p < 0.001$) between normal group and ≥75% stenosis group.

**DISCUSSION**

Echocardiographic detection of CAS is currently performed by gross visual observation of normal systolic LV wall motion defect induced by some form of exertional load. This method depends greatly on the experience of the operator, in addition to which adequate loading cannot be achieved in many patients. Detection based on resting images was tested to overcome this problem. We focused on 2D SR analysis, because it enables evaluation of LV wall motion in echocardiograms\(^{12}\). In SR analysis, both one-dimensional (tissue velocity imaging: TVI) and 2D methods are used, the former utilizing Doppler sonography unlike the latter. Several reports have explained the effectiveness of TVI using strain and SR methods for evaluation of regional wall motion in myocardial ischemia\(^{14\sim20}\). SR is the rate of change in velocity during a change in the distance between two points. It is obtained by differentiating the strain value as a function of time, i.e., the rate of change in the distance between the two points\(^{18,19}\). It is believed that SR is more suitable for the evaluation of local systolic function of the LV wall\(^{17\sim19}\). In consideration of these characteristics of strain and SR, the latter might be a sensitive indicator of ischemia.

1 2D SR method

Several features characterize 2D SR analysis: the ROI is set at the narrowest region along the LV endocardium, the sample point is placed automatically at the center of each segment, and the sample point automatically tracks myocardial speckles moving in 2D without reference to the direction of the incident ultrasound beam. If one sample point receives information from multiple myocardial speckles, EchoPAC PC determines whether the data can be analyzed and computes the SR. Any missing observation resulting from the failure in automatic tracking of some speckles is interpolated using the information from the remaining speckles. Thus, setting ROIs that allow automatic tracking reduces the failure rate to very low levels. That is, the 2D method allows measurement in sample
points by automatically tracking myocardial speckles based on their common end-systolic and end-diastolic location, which is unaffected by the distance from the ultrasound probe and the direction of the ultrasound beam. CAS is satisfactorily estimated by this method by drawing narrow ROIs over the subendocardial region in resting echocardiograms. Therefore, we chose the 2D SR method for the analysis of LV wall motion in this study. We have encountered a case showing normalized 2D SR after PCI and then newly progressed 75% stenosis detected by the discriminant function (Fig. 5). The fact that 75% stenosis was detected by this function clinically proved the experimental result that 50% coronary stenosis reduced coronary flow down to about 80%.21

2 Study limitation
We have described above how CAS can be detected with 2D SR analysis of resting echocardiograms. However, a few issues need to be addressed before this method can be applied clinically. The first issue is noise—although modern ultrasound imaging devices appear to be better at handling noise, there still are cases where echocardiograms cannot be evaluated in routine practice, necessitating the use of CAG or multidetector-row computed tomography (MDCT). Further advances in signal-to-noise ratio improvement in ultrasound imaging technology are eagerly awaited. The second issue is the recognition that SR parameters measure wall motion abnormality, but do not directly measure the ischemia. As far as we use our method to post-PCI patients, we do not meet this kind of issue of limitation. But when we use it to patients who did not undergo CAG, combined use with myocardial contrast echocardiography (MCE) is required to confirm myocardial ischemia as the cause of angina pectoris.22,23 Many investigators believe that MCE produces unstable images with poor reproducibility, and that it requires further technological improvement before it can be deemed suitable for diagnosing angina pectoris.

3 Reproducibility
Echocardiography in this study was performed by the same operator. Because the 2D SR method may be sensitive to noise, it is important to evaluate the reproducibility of this method. Thus, intra- and inter-operator reproducibility tests were performed, using the same patients with normal coronary arteries and single vessel disease. To determine intra-operator variability, the same operator examined each patient twice at an interval of 4 weeks. The reproducibility of the final evaluation (positive or negative of a given discriminant score “Z”) was 100%, although “Z” scores at the two examinations of the same patient were different (κ = 0.74, p < 0.001). The inter-operative test was performed by two cardiologists. Reproducibility was 89.9%. Eighteen patients were missed for the following reasons: failure to make an acceptable ROI in sixteen patients, and acceptable ROIs and wrong “Z” in two patients (κ = 0.97, p < 0.001). However, reproducibility of our method was satisfactory enough to permit clinical use of 2D SR analysis.

CONCLUSIONS
Most post-PCI patients are followed-up by CAG in about 6 to 12 months interval. But there are sometimes emergent PCI because of restenosis or new stenotic lesions. So non-invasive and easy-doing test which can be done frequently without a physician’s attendance, but has satisfactory diagnostic accuracy of significant stenosis of coronary artery is expected for post-PCI patients. For this purpose we employed 2D SR of resting echocardiography. In order to overcome the 2D SR drawbacks
Fig. 5 One of the example case in which the discriminant score “Z” detected significant coronary stenosis pre- and post-PCI

a) Pre-CAG SR: LAD “Z” = 2.10, RCA “Z” = 0.61, LCX “Z” = 2.76. Echocardiographical diagnosis was triple vessel disease. b) Diagnostic CAG; RCA #1: 75%, LCX distal #13: total occlusion, LAD #6: 75%. CAG showed triple vessel disease as detected by “Z” score. PCI was done to all of three lesions. c) Post-PCI SR: LAD “Z” = -5.09, RCA “Z” = -2.80, LCX “Z” = -2.04. d) SR; RCA “Z” = -0.71, LAD “Z” = -0.91, LCX “Z” = 1.92. CAG showed 75% stenosis at proximal #13 of LCX.
(too sensitive to catch noises and too complicated curve to be analyzed by single parameter as in strain curve) and make it clinically useful and valuable, we employed four parameters to created a discriminant function equation for $\geq 75\%$ stenosis by which the discriminant score (Z) was computed. The discriminant probability was 86.39% when a positive diagnosis was declared for $Z > 0$. Our method allows the detection of CAS with resting echocardiography, and it is accurate enough for clinical use. Thus, we concluded that patients after PCI can be followed-up more precisely by combining the discriminant function of non-stress echocardiography to CAG.

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