Sensitve Method of Detecting Myocardial Ischemia During Dobutamine Stress Echocardiography
— Assessment of Asynchrony in Early-Systolic Wall Motion —

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To test the hypothesis that dobutamine-induced myocardial ischemia causes early-systolic asynchrony predominantly in the regional left ventricular wall, color kinesis (CK) images during dobutamine stress echocardiography (DSE) were recorded in 13 patients with coronary artery disease and in 10 patients without, all of whom showed normal wall motion at rest. Based on the visual interpretation of DSE and the angiographic findings, 21 segments in the short-axis images at the papillary muscle level were defined as ischemic, and 60 segments of the patients without coronary artery disease were defined as normal. The incremental fractional segmental area change (IFAC) was calculated at 33-ms intervals from the CK images. At the peak dose, IFACs during the first 33 and 33–67 ms were significantly lower in the ischemic segments than in the normal ones, and IFACs during 133–167, 200–233 and 233–267 ms were significantly higher in the ischemic segments. The ratio (peak/low dose) of the cumulative fractional area change at 100 ms gave the best sensitivity (= specificity) for differentiating the 2 groups (86%). Dobutamine-induced ischemia is characterized by an early-systolic asynchrony rather than a change in overall wall excursion and CK can provide an objective assessment of ischemia developing during DSE. (Circ J 2003; 67: 317–322)

Key Words: Asynchrony; Color kinesis; Coronary artery disease; Dobutamine stress echocardiography

Dobutamine stress echocardiography (DSE) is acknowledged as a useful method for detecting myocardial ischemia2–4 risk stratification5 and assessing myocardial viability6–7 However, the interpretation of DSE remains qualitative and subjective, lowering the reproducibility of the results in either individual investigations or interinstitutional comparisons8,9 Thus, a quantitative and objective method of evaluating regional wall motion (RWM) during DSE is required.

Several experimental studies have demonstrated that a disturbance of left ventricular wall motion during early systole precedes a reduction in overall systolic wall motion in the sequence of events caused by myocardial ischemia10–17 Some clinical studies examining regional left ventricular wall motion at rest have also shown that a deterioration in early-systolic wall motion is common in patients with coronary artery disease (CAD).18–24 However, there is no evidence showing that stress-induced myocardial ischemia deteriorates early-systolic wall motion in the patient25

Color kinesis (CK) enables automatic tracking of endocardial motion throughout systole and encodes an individual color to a locus of the endocardium every 33 ms.26–29 Although the segmental analysis of CK images has been used during DSE to detect the reduced magnitude of wall excursion,26 the usefulness of this method for analyzing the timing of endocardial motion during DSE has not been evaluated.

The present study was designed to test the hypothesis that dobutamine-induced myocardial ischemia causes predominantly early-systolic deterioration in left ventricular wall excursion.

Methods

Subjects
Twenty-three subjects were selected from the patients who fulfilled the following criteria: (1) admitted to Hokkaido University Medical Hospital for coronary angiography to evaluate chest pain, (2) without any wall motion abnormality on baseline 2-dimensional (D) echocardiography, (3) with adequate short-axis echocardiographic images at the level of papillary muscle throughout the dobutamine stress testing, (4) with no relevant organic heart disease other than CAD, and (5) in sinus rhythm. There were 13 patients with CAD (61±11 years old, 11 males) who were judged as having wall motion abnormalities in the territory of a significantly stenotic coronary artery during DSE from visual analysis of short-axis images at the level of the papillary muscle. Coronary angiography revealed 1-vessel disease in 6 of the 13 patients, 2-vessel disease in 6, and 3-vessel disease in 1. A left anterior descending artery stenosis was shown in 7 patients, left circumflex artery stenosis...
Dobutamine was intravenously administered at an initial dose of 5 μg·kg⁻¹·min⁻¹ and the dose was increased to 10, 20, and 30 μg·kg⁻¹·min⁻¹ for at least 3 min in each stage. In patients not achieving 85% of their age-predicted maximal heart rate, atropine was given intravenously with the continuation of dobutamine, starting with 0.25 mg and repeated up to a maximum of 1.0 mg. The criteria for stopping dobutamine infusion included (1) achievement of 85% of the predicted maximum heart rate, (2) newly developed wall motion abnormalities, (3) ST-segment depression or elevation >0.2 mV on electrocardiogram (ECG), (4) chest pain, (5) systolic blood pressure >220 mmHg, (6) decrease in systolic pressure >20 mmHg compared with the previous step, (7) significant ventricular or supraventricular arrhythmias, or (8) serious side effects of dobutamine.

Table 1  Hemodynamic Data of the Patients With and Without CAD During DSE

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>Systolic blood pressure (mmHg)</th>
<th>Diastolic blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Low dose</td>
<td>Peak dose</td>
</tr>
<tr>
<td>With CAD</td>
<td>61±7</td>
<td>80±14</td>
<td>109±14</td>
</tr>
<tr>
<td>Without CAD</td>
<td>59±9</td>
<td>77±16</td>
<td>112±20</td>
</tr>
</tbody>
</table>

In all variables, there was no statistically significant difference between the patients with and without CAD. CAD, coronary artery disease; Low dose/peak dose, dose of dobutamine.
between groups using an unpaired t test. Each of IFACs and FACs at the peak dose was compared with that at the low dose in the 2 groups using a paired t test. To assess the temporal changes in these parameters with the dose of dobutamine in individual segments, we employed the ratio of the value at peak dose to that at low dose. For this purpose, a low dose of dobutamine was defined as 10\( \mu \)g kg\(^{-1} \) min\(^{-1} \) because all of the ischemic segments in this study developed abnormal wall motion at 20\( \mu \)g kg\(^{-1} \) min\(^{-1} \) or more. The ratios (peak/low dose) of these parameters were compared between groups using an unpaired t test.

To test the discriminatory ability in detecting ischemic segments, sensitivity/specificity curves and receiver operating characteristic (ROC) curves were constructed. Plotting the sensitivity and specificity against the whole range of the measured values, the best cutoff value and the sensitivity (= specificity) were determined as the coordinates of the intersection of these 2 curves. Comparison of areas under the ROC curves was performed by the method of Hanley and McNeil with a 2-tailed z statistic, using the freeware program, ROCKIT, of Metz et al.\(^{30} \) All data are expressed as mean±SD. Differences were considered significant at p<0.05 in all the comparisons in this study.

**Results**

Hemodynamic data during DSE are shown in Table 1. Heart rate, systolic and diastolic blood pressures at each

![Fig 2. Color kinesis images during dobutamine stress echocardiography. The upper panel shows images obtained from a patient with normal wall motion and the lower panel shows those from a patient with dobutamine-induced ischemia in the posterior wall (arrows). In each panel, the image at baseline (Left), low dose dobutamine (Middle) and peak dose dobutamine (Right) are shown.](image)

![Fig 3. Incremental fractional area changes (IFAC) measured at 33-ms intervals during systole in the normal and ischemic segments at baseline (A) and low dose (B) and peak dose of dobutamine (C). *p<0.05; †p<0.01; ‡p<0.001 vs normal segments.](image)

Table 2 Comparisons Between Selected Parameters at Low and Peak Dose of Dobutamine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low dose</th>
<th>Peak dose</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFAC (0–33 ms) (%)</td>
<td>14.1±8.0</td>
<td>22.6±12.1*</td>
<td>15.5±8.7</td>
</tr>
<tr>
<td>IFAC (33–67 ms) (%)</td>
<td>15.2±6.8</td>
<td>22.4±9.0†</td>
<td>15.3±7.0</td>
</tr>
<tr>
<td>FAC67 ms (%)</td>
<td>29.5±11.8</td>
<td>45.0±15.1*</td>
<td>31.0±10.9</td>
</tr>
<tr>
<td>FAC100 ms (%)</td>
<td>43.8±13.9</td>
<td>62.1±14.2*</td>
<td>45.9±14.2</td>
</tr>
<tr>
<td>FACes (%)</td>
<td>85.6±9.7</td>
<td>91.2±8.1*</td>
<td>85.4±12.3</td>
</tr>
</tbody>
</table>

IFAC, incremental fractional area change; FAC, fractional area change; es, end-systole. *p<0.001 vs low dose; †p<0.0001 vs normal segments.
higher than at the low dose in the normal segments, whereas no significant difference was observed in the ischemic segments (Table 2). The peak/low-dose ratios of IFAC (33–67 ms), FAC67 ms, FAC100 ms and FACes in the ischemic segments were significantly lower than in the normal segments (Table 3).

The results of the ability of these parameters to discriminate between ischemic and normal segments are summarized in Table 4. Among the early-systolic parameters, each area under the ROC curve for FAC67 ms and FAC 100 ms at the peak dose and the ratio of those were significantly greater than that for FACes at the peak dose. Among these parameters, the ratio of FAC100 ms gave the best sensitivity (= specificity) of 86% at the cutoff value of 1.18 (Figs 4, 5).

### Discussion

The present study revealed that dobutamine-induced transient myocardial ischemia is characterized by a reduction in the early-systolic excursion of the regional left ventricular endocardium and an enhanced excursion during mid-to-late systole. We also found that asynchronous wall motion in early systole detected by the segmental analysis of CK images is a more sensitive marker of induced ischemia than a reduction in the overall magnitude of the systolic excursion. Because myocardial wall motion in the ischemic segments at the peak dose of dobutamine was impaired during the first 100-ms of systole, we tested the ability of the early-systolic parameters to differentiate the ischemic segments from the normal segments perfused by normal coronary arteries. FAC at 67 ms after end-diastole (FAC67 ms) and at 100 ms (FAC100 ms) were proven to more accurately discriminate between the 2 groups than FAC at end-systole (FACes). To reduce the influence of cardiac translation during systole, we employed the ratio (peak/low dose) of FAC67 ms and FAC100 ms in individual segments and found that the ratio of FAC100 ms was the most sensitive and specific among all indexes examined in this study for detecting wall motion abnormalities caused by ischemia during DSE.

Wiegner et al have shown, in an isolated muscle preparation, that hypoxic muscle is characterized by impaired development of the contractile force and that early shortening declines rapidly with hypoxia. Another study revealed decreased myocardial contraction during the prejection and ejection phases and enhanced velocity of postejection shortening in experimental animals at a relatively early time point of myocardial ischemia. It is thought that the early phase of systole is vulnerable to passive stretching during ischemia because the peak wall stress occurs late in the prejection phase or early in the ejection phase and that preserved myocardial shortening occurs after the reduction of wall stress, resulting in an exaggerated shortening during late systole.

Several clinical studies based on cineventriculography or radionuclide angiography have also demonstrated the predominantly early-systolic akinesis or even paradoxical motion of the ischemic wall, followed by an exaggerated shortening during late systole. However, most of those

### Table 3 Ratio (Peak/Low Dose) of Selected Parameters in Normal and Ischemic Segments

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal segments (Mean±SD)</th>
<th>Ischemic segments (Mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio of IFAC (0–33 ms)</td>
<td>1.20±0.97</td>
<td>1.29±0.97</td>
</tr>
<tr>
<td>Ratio of IFAC (33–67 ms)</td>
<td>1.71±0.89</td>
<td>1.67±0.59</td>
</tr>
<tr>
<td>Ratio of FAC67 ms</td>
<td>1.49±0.30</td>
<td>0.93±0.37</td>
</tr>
<tr>
<td>Ratio of FAC100 ms</td>
<td>1.07±0.09</td>
<td>0.96±0.16</td>
</tr>
</tbody>
</table>

IFAC, incremental fractional area change; FAC, fractional area change; es, end-systole. *p<0.001 vs normal segments.

### Table 4 Sensitivity and Specificity for the Detection of Ischemic Wall Motion Abnormality and Results of Receiver Operating Characteristic Analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value at peak dose</th>
<th>Ratio (peak/low dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Se=Sp (%)</td>
<td>AUC (%)</td>
</tr>
<tr>
<td>IFAC (0–33 ms)</td>
<td>62</td>
<td>0.73</td>
</tr>
<tr>
<td>IFAC (33–67 ms)</td>
<td>73</td>
<td>0.82</td>
</tr>
<tr>
<td>FAC67 ms</td>
<td>77</td>
<td>0.85*</td>
</tr>
<tr>
<td>FAC100 ms</td>
<td>75</td>
<td>0.83*</td>
</tr>
<tr>
<td>FACes</td>
<td>55</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Se, sensitivity; Sp, specificity; AUC, area under the receiver operating characteristic curve; IFAC, incremental fractional area change; FAC, fractional area change; es, end-systole. *p<0.05 vs FACes at peak dose.

Fig4. Sensitivity/specificity curves for detecting ischemic wall motion abnormality as a function of the cutoff point for FAC100 ms at the peak dose of dobutamine (A), the ratio (peak/low dose) of FAC100 ms (B), FACes at the peak dose (C) and the ratio of FACes (D). The best cutoff point is determined as the point of intersection of the 2 curves. Abbreviations as in Table 4.

Fig5. Receiver operating characteristic curves for comparison of the diagnostic power of FAC100 ms and FACes at the peak dose of dobutamine, and the ratio (peak/low dose) of those parameters. Abbreviations as in Table 4.
studies were carried out in heterogeneous populations that included many patients with previous myocardial infarction. Zeiher et al, using an automated contour detection on 2-D echocardiograms, assessed regional contraction in patients with unstable angina during transient myocardial ischemia and reported that transient ischemia did not lead to early-systolic wall motion abnormality, but caused predominantly mid-to-late systolic abnormal synergy. Tashiro et al divided the systolic interval into 3 periods and measured the percentage hemiaxis shortening of each left ventricular segment using manual tracing of the 2-D echocardiograms of patients with CAD during exercise-induced ischemia. Left ventricular wall motion was defined as abnormal when at least one of those 3 periods shows deterioration in systolic shortening. Such an integration method more sensitively detected regional ischemia than the simple comparison between end-diastolic and end-systolic frames. However, impaired shortening in early systole was not common to the ischemic left ventricular segments in their study.

The present study is consistent with the results of Zeiher et al and Tashiro et al insofar as detection of temporal abnormalities in ventricular contraction provided a better means of assessing myocardial ischemia. However, as far as we know, this is the first report demonstrating that in clinical patients stress-induced myocardial ischemia causes deterioration of the early-systolic wall excursion predominantly. The difference in the method of inducing ischemia is conceivably the cause of the discrepancy among these 3 studies. Dobutamine increases myocardial contractility to a greater extent than exercise or the resting condition, resulting in exaggerated early shortening in the normal segment and a rapid increase in intracavitary pressure. Consequently, an early-systolic asynchrony might be most prominent in DSE.

There have been several studies aimed at quantifying RWM during DSE using new echocardiographic technologies. Some investigators used tissue Doppler imaging and reported the usefulness of myocardial velocity measurements by pulsed-wave or M-mode tissue Doppler for the detection of myocardial ischemia and viability. Strain rate imaging, as well as tissue Doppler imaging, might contribute to the development of a system for objective interpretation of stress echocardiography, but are essentially angle-dependent methods despite several efforts to overcome this limitation. CK can visualize spatial and temporal information about left ventricular endocardial motion independent of the angle. Lang et al first documented the usefulness of digital analysis of CK images for the quantitative evaluation of left ventricular RWM and Koch et al applied this method to DSE and demonstrated the usefulness of the fractional segmental area change at end-systole to detect RWM abnormalities. Our study extends their results, and demonstrates that the early-systolic asynchrony detected on CK images could be a more sensitive marker of myocardial ischemia induced by dobutamine than the reduction in the overall magnitude of the systolic excursion. Such semi-automated methods during DSE might contribute to the quantitative and objective detection of CAD.

Study Limitations
Stress-induced myocardial ischemia was not confirmed by other diagnostic techniques, such as radionuclide examination, in this population of patients. In most of the patients with CAD, the stress-induced wall motion abnormalities occurred at relatively high heart rate and further investigations may be necessary to elucidate whether the early-systolic parameter in this study can reasonably detect the myocardial ischemia induced at a lower heart rate.

In this study, the CK images were analyzed only in the short-axis view. The ability of the new parameters to discriminate between ischemic and normal segments as defined in the study cannot be extrapolated to the accuracy of the technique for detecting myocardial ischemia in the clinical setting. To determine the clinical significance of this method, further investigations in a larger cohort of patients are recommended.

Although the endocardial border was successfully tracked even with fundamental imaging in the selected population of this study, the tracking of the entire endocardial border on CK images is sometimes suboptimal in the clinical setting. Further advances in ultrasound technology, such as tissue harmonic imaging or contrast echography, are necessary to facilitate endocardial tracking. Although we intended to automatically analyze RWM, our method still has some manually operated procedures; viz, the CK program itself requires manual adjustment of the time–gain compensation and lateral gain control, and the CK images have to be transferred to another computer to obtain the segmental fractional area changes after the examination. Recently, Fujino et al developed an automated segmental motion analysis system to provide real-time and on-line objective assessment of regional wall excursion and such a system should be used to establish the objective interpretation of DSE.

Conclusions
The results of this study demonstrate that dobutamine-induced myocardial ischemia is characterized by a reduction in early-systolic wall excursion and an enhanced excursion during mid-to-late systole. The ratio (peak/low dose) of FAC_{100ms} during DSE sensitively detects stress-induced myocardial ischemia. These findings provide a basis for developing an automated system that objectively detects CAD during stress echocardiography.

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References


