Effects of Postischemic Regional Left Ventricular Diastolic Wall Motion Abnormalities or Delayed Relaxation Following Coronary Vasospasm on Global Diastolic Function

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Background  Regional left ventricular (LV) diastolic wall motion abnormalities detected by color kinesis (CK), an echocardiographic technique, may be a more sensitive measure to postischemic damage following coronary spasm than parameters of global diastolic function.

Methods and Results  Regional LV diastolic wall motion was evaluated by using CK in 18 patients with variant angina on the day following coronary spasm, which was induced by intracoronary acetylcholine. Fractional regional LV cavity area expansion in the short-axis view during the first 30% of the LV filling time, was used to identify postischemic asynchronous diastolic wall motion. Regional delayed relaxation was observed in any of the LV regions in all the patients, who were divided into 2 groups (Group S: 7 patients with single-vessel spasm with regional delayed relaxation in one area. Group M: 11 patients with multivessel spasm or spasm of the proximal left anterior descending branch with regional delayed relaxation in multiple areas). In Group S, no abnormality (0%) was noted in any of the indexes of global diastolic function including the isovolumic relaxation time, the ratio of peak rapid filling to peak atrial filling velocities and the deceleration time. In contrast, in 5 (45%) of the Group M patients, abnormalities were noted in all of those indexes.

Conclusions  Postischemic regional LV-delayed relaxation following coronary vasospasm was detected sensitively by analysis of CK images. The indexes of global LV diastolic function are insensitive to postischemic damage following single vessel spasm, although they are somewhat sensitive following multivessel spasm.

Key Words: Color kinesis; Coronary vasospasm; Diastolic dysfunction; Global diastolic function; Regional diastolic function

Abnormalities of left ventricular (LV) filling and relaxation are sensitive early signs of myocardial ischemia in acute experiments involving animals and humans. It is reasonable to assume that good quantitative analysis methods should detect differences between ischemic and non-ischemic myocardium very accurately. A number of non-invasive indexes of diastolic function have been proposed by the analysis of M-mode echocardiograms, Doppler LV filling velocity patterns, and radionuclide ventriculograms. Diastolic function as assessed with these indexes is frequently abnormal, even in patients with ischemic heart disease in whom systolic function is maintained within normal ranges. Indeed, the beginning of the regional LV outward wall motion in the isovolumic relaxation phase is delayed in the coronary involved region. Because the impaired region is confined to the underperfused area of the involved coronary arteries, and ischemic damage may not necessarily result in impaired global LV diastolic function; the measure of the LV regional diastolic function may provide a more sensitive estimate of the coronary involved region than the measure of global LV function.

Color kinesis (CK; Philips Medical Systems, Andover, MA, USA) has been recently developed to facilitate the echocardiographic evaluation of regional wall motion. Recently, we have found using this method, that impaired or stunned regional diastolic function with delayed outward wall motion persisted beyond recovery of ischemia commonly in patients with coronary vasospasm. This diastolic dysfunction is specifically caused by postischemic damage because it is completely recovered. The present study was designed to determine how the global diastolic function was affected by impaired regional LV wall motion or diastolic asynchrony following coronary vasospasm in patients with single or multivessel coronary vasospasm.

Methods

Study Patients  Consecutive 18 patients (11 men and 7 women with a mean age of 62±9 years; range: 37–77 years) with variant angina having a recent history of repetitive angina, coronary vasospasm induced by intracoronary injection of acetylcholine during coronary arteriography, good echocardiographic image quality and adequate tracking by CK but without any types of arrhythmias or conduction disturbance, were subjected to the present study. Patients with a significant (>75% luminal diameter) organic coronary stenosis or apparent systolic regional LV dysfunction were
not included in the present study. Some patients had been involved in previously reported studies.\textsuperscript{12-14} In all patients, coronary artery spasm (transient total or subtotal occlusion) associated with ST segment elevation (≥0.1 mV) on the electrocardiogram and/or typical chest pain was angiographically demonstrated in at least one of the major coronary arteries during angina and was provoked by an intracoronary injection of acetylcholine.\textsuperscript{15} The spasm was relieved spontaneously within 2 min or otherwise by intracoronary administration of isosorbide dinitrate. Patients with regional delayed relaxation found by the CK study, but without spasm induced by acetylcholine in the coronary artery perfusing the region, were not included in the present study. For the control, age- and sex-matched 12 subjects (7 men and 5 women, mean age: 60±11 years) were also studied for CK study. All the study patients had no abnormalities in echocardiographic parameters including the LV end-diastolic diameter, fractional shortening, LV thickness and the calculated LV mass index. Written informed consent was obtained from all the study patients, and the study protocol was approved by the ethics committee of our institution.

**CK Study**

The first CK study was performed within 2 weeks of the last angina and the second one on the day following the provoked spasm during the coronary arteriographic examination, which was undertaken within a week of the first CK study. Diastolic CK images were obtained by using a commercially available ultrasound system (SONOS 5500, Philips Medical Systems, Andover, MA, USA). A custom software program was used to extract endocardial expansion for myocardial segments in the LV midpapillary short-axis view, as reported previously.\textsuperscript{12-14,16,17} The timing of color encoding was set to begin at the first frame in which outward endocardial motion was noted, and its duration was set to its maximal value (33 ms×19 frames). The sites of regional LV diastolic wall motion or regions of interest were set on the basis of standard segmentation models corresponding to the 3 major coronary perfusion territories assigned as follows (Fig 1): (i) the anterior and anteroseptal segments (AS) to the left anterior descending coronary artery (LAD); (ii) the anterolateral and posterolateral free wall segments (LAT) to the left circumflex branch (LCX) or the diagonal branches originated from LAD; and (iii) the posteroseptal and inferior segments (INF) usually to the right coronary artery (RCA). The CK-diastolic index was defined as the LV segmental cavity area expansion during the first 30% of diastole, divided by the segmental end-diastolic LV cavity area expansion, expressed as a percentage. The mean CK-diastolic indexes in 40 age-matched control subjects were 71±6, 72±7 and 75±7% in the territory of AS, LAT and INF, respectively.

![Diagram of CK-diastolic index](image)

**CK-diastolic index**

\[
\text{CK-diastolic index} = \frac{b}{a} \times 100\% 
\]

Fig 1. Segmental schemes and conceptual framework of the color kinesis (CK) used for the analysis of left ventricular (LV) endocardial wall motion in the short-axis view (modified with permission).\textsuperscript{14} The 3 sites, the anteroseptal (AS), the lateral (LAT), and the inferior (INF) segments, were set. The thickness of each band represents the outward motion of the individual segment during the specific interval (33 ms each). The CK-diastolic index was determined as the calculated LV segmental cavity area expansion during the first 30% of diastole, divided by the segmental end-diastolic LV cavity area expansion, expressed as a percentage. The dotted line shows the endocardial contour after the first 30% of diastole. ROI, region of interest.

**Doppler Analysis**

The Doppler study was performed at the same time as the CK study. Isovolumic relaxation time was measured as the time interval between the aortic valve closure and the onset of the mitral valve inflow. Peak velocities during rapid filling (E) and atrial contraction (A) were measured. Subsequently, the early-to-late diastolic mitral flow velocity (E/A) ratio was calculated, and the deceleration time was measured.

**Follow-up Data**

The study patients were followed up while taking medi-
cation including calcium entry blockers (usually 100 mg of long-acting diltiazem twice a day) with or without long acting nitrates. The CK study was repeated 2 and 4 weeks after the coronary vasospasm was induced by an intracoronary injection of acetylcholine.

Statistical Analysis

Results of analyses are expressed as mean ± standard deviation. Comparisons of the CK-diastolic indexes between groups were performed by using the Student’s unpaired t-test. Time-course comparisons of the CK-diastolic indexes were performed with ANOVA followed by the Student’s paired t-test. A p value <0.05 was considered to be statistically significant.

Results

Regional Diastolic Function

In all the study patients, coronary artery spasm was angiographically demonstrated in at least one of the major coronary arteries during angina, which was provoked by an intracoronary injection of acetylcholine. A multivessel spasm was induced in 8 (47%) patients. In the CK study, on the day following the coronary vasospasm, which was induced by an intracoronary injection of acetylcholine, regional delayed relaxation (CK-diastolic index <55%) was observed in the 31 territories perfused by the angina-provoking coronary arteries in all study patients. Each study patient had regional delayed relaxation in at least one of the AS, LAT and INF. The CK-diastolic index in each coronary perfusion territory and the angiographically demonstrated spasm arteries in the study patients are listed in Table 1. The mean CK-diastolic index was 32±7% in these territories, which was quite similar to that obtained before the coronary arteriography (31±8%). Study patients were divided into 2 groups: (i) Group S: 7 patients with single vessel spasm with regional delayed relaxation in one area; and (ii) Group M: 11 patients with multivessel spasm or spasm of the proximal portion of LAD with regional delayed relaxation in multiple areas.

Global Diastolic Function

Any of the indexes, isovolumic relaxation times, E/A ratios or deceleration times obtained from pulsed Doppler echocardiography of mitral valve inflow were not significantly different between the study patients and control subjects, and showed no apparent global diastolic dysfunction in the study patients (Table 2). Although all these values were significantly different between Group M and Group S, no significant differences were noted in any of these values between Group M and control subjects, except in terms of the isovolumic relaxation time (p<0.05). The

Table 1 Global and Regional Diastolic LV Function in Patients With Single and Multivessel Coronary Vasospasm

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Sex</th>
<th>Coronary spasm</th>
<th>CK-diastolic index (%)</th>
<th>Global LV diastolic indexes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>LAD</td>
<td>LCX</td>
<td>RCA</td>
</tr>
<tr>
<td>Group S</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>65</td>
<td>F</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>M</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>M</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>M</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>57</td>
<td>M</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>59</td>
<td>F</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>M</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Group M

| 8           | 58  | M   | +   | –   | –   | 28 | 40  | 87  | 78       | 1.2       | 170     |
| 9           | 72  | F   | +   | –   | –   | 30 | 70  | 74  | 124      | 0.7       | 290     |
| 10          | 76  | M   | +   | –   | –   | 22 | 77  | 68  | 132      | 0.6       | 300     |
| 11          | 59  | M   | +   | –   | –   | 23 | 33  | 90  | 90       | 1.0       | 184     |
| 12          | 59  | F   | +   | –   | +   | 40 | 73  | 40  | 132      | 0.7       | 207     |
| 13          | 65  | M   | +   | –   | +   | 29 | 78  | 78  | 86       | 0.9       | 210     |
| 14          | 37  | F   | +   | –   | +   | 26 | 76  | 52  | 83       | 1.1       | 140     |
| 15          | 77  | F   | +   | –   | +   | 39 | 75  | 75  | 120      | 0.6       | 290     |
| 16          | 65  | M   | +   | –   | +   | 33 | 38  | 80  | 78       | 1.0       | 204     |
| 17          | 57  | F   | +   | –   | +   | 37 | 90  | 38  | 88       | 1.1       | 186     |
| 18          | 65  | M   | +   | –   | +   | 32 | 74  | 74  | 122      | 0.5       | 295     |

LAD, left anterior descending coronary artery; LCX, left circumflex branch; RCA, right coronary artery; AS, anteroseptal segment; LAT, lateral segment; INF, inferior segment; IRT, isovolumic relaxation time; DT, deceleration time.

Table 2 Global Diastolic Function Parameters by Doppler Echocardiography on the Day Following Coronary Spasm

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>IRT (ms)</th>
<th>E/A ratio</th>
<th>DT (ms)</th>
<th>E (cm/s)</th>
<th>A (cm/s)</th>
<th>HR</th>
<th>SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects</td>
<td>12</td>
<td>86±12</td>
<td>1.02±0.22</td>
<td>194±21</td>
<td>70±19</td>
<td>69±16</td>
<td>66±9</td>
<td>122±15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Patients with variant angina (total)</td>
<td>18</td>
<td>94±21</td>
<td>0.94±0.21</td>
<td>205±51</td>
<td>67±16</td>
<td>71±17</td>
<td>67±8</td>
<td>121±15</td>
</tr>
<tr>
<td>Group S</td>
<td>7</td>
<td>77±4</td>
<td>1.07±0.11</td>
<td>17±125</td>
<td>71±15</td>
<td>67±15</td>
<td>67±9</td>
<td>120±14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p&lt;0.01</td>
<td>p&lt;0.05</td>
<td>p&lt;0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Group M</td>
<td>11</td>
<td>103±22</td>
<td>0.85±0.23</td>
<td>225±55</td>
<td>62±18</td>
<td>73±15</td>
<td>68±10</td>
<td>123±13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p&lt;0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

IRT, isovolumic relaxation time; DT, deceleration time; E, E velocity; A, A velocity; HR, heart rate; SBP, systolic blood pressure.
incidences of a prolonged isovolumic relaxation time (>110 ms), a decreased E/A ratio (<0.9) and a prolonged deceleration time (>220 ms) were 45, 45 and 36% in Group M patients, respectively, while none of them (0%) were noted in any of the patients from Group S (Table 3).

Typical CK images and pulsed Doppler echocardiograms of mitral valve inflow from study patients are shown in Fig 2–4.

Table 3  Sensitivity of Global Diastolic Function Parameters by Doppler Echocardiography on the Day Following Coronary Spasm for the Detection of the Post-Ischemic Stunned Myocardium

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>IRT &gt;110 ms</th>
<th>E/A ratio &lt;0.9</th>
<th>DT &gt;220 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with variant angina</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>5 (28%)</td>
<td>5 (28%)</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Group S</td>
<td>7</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Group M</td>
<td>11</td>
<td>5 (45%)</td>
<td>5 (45%)</td>
<td>4 (30%)</td>
</tr>
</tbody>
</table>

IRT, isovolumic relaxation time; DT, deceleration time.

Fig 2. End-diastolic color kinesis (CK) images in the short-axis view obtained in patient 7 on the day following left anterior descending coronary artery (LAD) spasm induced by an intracoronary injection of acetylcholine. The dotted line shows the endocardial contour after the first 30% of diastole. Note the presence of a thick yellow band in anteroseptal (AS) in late diastole, which reflects the greater dependence of left ventricular (LV) filling on atrial contraction. The global diastolic indexes obtained by the Doppler technique include the isovolumic relaxation time, the early-to-late diastolic mitral flow velocity (E/A) ratio and the deceleration time remained within normal limits.

Fig 3. End-diastolic color kinesis (CK) images in the short-axis view obtained in patient 17 on the day following left anterior descending coronary artery (LAD) and right coronary artery (RCA) spasm, separately induced by an intracoronary injection of acetylcholine. The dotted line shows the endocardial contour after the first 30% of diastole. Note the presence of a thick yellow band in both anteroseptal (AS) and inferior (INF) segments in late diastole. The global diastolic indexes obtained by Doppler technique including the isovolumic relaxation time, the early-to-late diastolic mitral flow velocity (E/A) ratio and the deceleration time remained within normal limits.

59 M

CK-diastolic index

<table>
<thead>
<tr>
<th></th>
<th>AS</th>
<th>LAT</th>
<th>INF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23</td>
<td>80</td>
<td>72 (%)</td>
</tr>
</tbody>
</table>

Isovolumic relaxation time: 76 ms
E/A ratio: 1.2
Deceleration time: 180 ms

57 F

CK-diastolic index

<table>
<thead>
<tr>
<th></th>
<th>AS</th>
<th>LAT</th>
<th>INF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21</td>
<td>90</td>
<td>38 (%)</td>
</tr>
</tbody>
</table>

Isovolumic relaxation time: 88 ms
E/A ratio: 1.1
Deceleration time: 186 ms

Time-Course of CK-Diastolic Indexes

The repeated CK study was conducted after a 2-week (14±1 days) and a 4-week (28±2 days) angina-free period under medication. The mean CK-diastolic index was 33±7% in the 24 territories perfused by the angina-provoking coronary arteries on the day following the induced spasm. The index significantly (p<0.01) improved after 2 weeks (56±10%) and increased to 71±8% after 4 weeks. No significant change was noted in the heart rate of patients.
Discussion

Regional Diastolic Stunning as a Sensitive Marker for Recent Myocardial Ischemia

Recently, we have reported that regional delayed relaxation or tardorelaxation was observed after the occurrence of spasm in patients with variant angina or coronary spastic angina, and that these abnormalities persisted for a few weeks. Delayed recovery of regional systolic function in spite of normal perfusion after transient, severe ischemia or ischemia–reperfusion has been recognized as myocardial stunning. It has been reported that diastolic dysfunction persisted seconds or minutes beyond the recovery of normal systolic function after brief coronary occlusion, and hours or days after exercise-induced severe ischemia. Repeated severe ischemia caused by spasm may contribute to prolonged diastolic stunning in patients with variant angina.

Postischemic Global vs Regional Diastolic Function Following Coronary Spasm

Sasayama et al observed that significant regional asynchrony during isovolumic relaxation, contributing to prolongation of the isovolumic relaxation time, developed in response to pacing-induced ischemia. In many patients with coronary artery disease and normal LV systolic function, impaired global diastolic filling may result from asynchronous LV regional diastolic function, which is a reversible manifestation of myocardial ischemia. In contrast, the present study demonstrated that none of the mitral Doppler indices including isovolumic relaxation times, transmural E/A ratios and deceleration times differentiated patients following single vessel coronary vasospasm from control subjects. In patients with multivessel spasm, abnormal values were sometimes noted in those indexes but in no more than half of the cases. Global diastolic dysfunction observed during ischemia may be rapidly attenuated after ischemia. In cases of coronary artery disease, the impaired region is confined within the perfused area of the involved coronary arteries. Subsequent ischemic damage, if small, may not necessarily result in impairment of global LV diastolic function. The measure of the LV regional diastolic function may provide a more sensitive estimate of the coronary involved region than that of global LV function. The regional impairment of diastolic wall motion was returned to normal after a 4-week angina-free period in most of the study patients, possibly reflecting postischemic myocardial stunning. This impairment had already been noted before the spasm was induced during coronary arteriography, suggesting that stunned diastolic function have been present probably because of a spontaneously-occurring coronary spasm prior to the present study.

Mechanism of Diastolic Stunning in Patients With Coronary Vasospasm

Although oxygen-derived free radicals concomitant with calcium overload during the early reperfusion period have been suggested to be important mediators of myocardial systolic stunning after temporary coronary flow obstruction, less information is available about the mechanism of diastolic stunning. The early phase of myocardial relaxation, referred to as isovolumic relaxation, is an active process during which calcium is removed from the cytoplasm surrounding the myofibrils. Dysfunctional calcium uptake by the sarcoplasmic reticulum or impaired myocyte calcium handling may have caused slowing of the diastolic relaxation blunting, early diastolic regional wall motion after angina or ischemia–reperfusion in patients with coronary vasospasm. Repair of proteolytic damage including new protein synthesis relating to calcium handling may play a role in the delayed or slow recovery of diastolic function.

Clinical Implications

The detection of regional wall motion abnormalities during diastole or delayed relaxation by CK is a sensitive and specific method to uncover myocardial ischemia. The site of regional delayed relaxation coincided well with the area perfused by the angina-provoking vessel, as revealed by the intracoronary infusion of acetylcholine. This non-invasive diagnostic test for coronary vasospasm can be conducted safely during attack-free periods. Repeated use of this test may allow the possibility of achieving complete differential.
diagnosis of chest pain syndrome in routine daily practice. Multivessel coronary spasm can also be diagnosed non-invasively during angina-free periods by using this technique. Previously, Kondo et al suggested that digital subtraction, high-frame-rate echocardiography may provide another non-invasive and accurate measure for visualization of regional LV relaxation abnormalities, although this method is only exclusively available in limited institutions. Recently, tissue Doppler imaging to create a myocardial velocity profile and gradient has been developed to facilitate the quantitative assessment of regional LV myocardial function and may be useful in the detection of regional diastolic stunned myocardium.

Study Limitations

The perfusion territory of LCX and the diagonal branches of LAD often overlap in the short-axis view of the echocardiographic image. Therefore, it is quite difficult to diagnose and differentiate spasm of LCX from spasm of LAD involving diagonal branches originating from the main branch of LAD, if LAD spasm is combined. Asynchronous LV relaxation may exist in patients with other cardiac diseases, such as idiopathic cardiomyopathy and hypertensive heart disease. Differential diagnosis from multivessel coronary spasm may be required in these cases.

Conclusions

Transient severe regional myocardial ischemia in patients with coronary vasospasm impairs regional diastolic wall motion, and this impairment persists even after perfusion has been restored. In contrast, the indexes for global diastolic function are insensitive as a postischemic marker, especially in cases of single vessel spasm. Echocardiographic evaluation of regional myocardial wall motion by CK is a useful non-invasive method for detection of prolonged postischemic diastolic dysfunction or stunning and for the identification of the angina-provoking vessel.

References

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