Utility of Combined Assessment of Coronary Flow Velocity and Myocardial Perfusion During Low-dose Dobutamine Stress Echocardiography in the Detection of Left Anterior Coronary Artery Disease

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Abstract

Background. Ischemia produces a sequence of events beginning with a decline in coronary flow reserve, myocardial perfusion abnormalities, and wall motion abnormalities. We hypothesized that low-dose dobutamine stress, combined with myocardial contrast echocardiography (MCE) and transthoracic Doppler echocardiography (TTDE), could detect myocardial ischemia preceding wall motion abnormalities according to this ischemic cascade.

Methods. Ninety-six patients suspected of having stable angina pectoris underwent TTDE, MCE, and semi-quantitative dobutamine stress echocardiography (Semi-DSE). Wall motion was assessed using a scoring system. The contrast agent, Levovist, was injected intravenously to assess the coronary flow velocity (CFV) ratio in the left anterior descending coronary artery (LAD) and myocardial perfusion abnormalities in the LAD territory. The CFV ratio was calculated as the CFV during low-dose dobutamine stress divided by the baseline CFV. Time-intensity data for MCE were fitted for y = A (1 - e^(-t)) from which the rate of the intensity rise (g) was calculated and the ratio was derived at baseline and during stress.

Results. Semi-DSE and low-dose dobutamine stress combined with TTDE and MCE were obtained successfully in 85 patients. The sensitivity and specificity of Semi-DSE for detecting >75% LAD stenosis were 79% and 93%, respectively. In the LAD territory, Semi-DSE showed 6 false negative and 4 false positive findings. However, failures of the CFV ratio and g ratio to increase >1.81 and >1.23 times that at baseline, respectively, indicated the presence of critical LAD stenosis, especially in 3 out of 6 false negative cases.

Conclusions. Low-dose dobutamine stress combined with TTDE and MCE is a useful method for detecting critical LAD stenosis during Semi-DSE. This method overcomes the limitations of Semi-DSE.

Key words: stress echocardiography (dobutamine), myocardial contrast echocardiography, transthoracic Doppler echocardiography, coronary artery disease

Introduction

The detection and evaluation of coronary artery disease (CAD) require some form of stress because autoregulation of flow in the coronary circulation prevents the myocardium from developing ischemia until coronary stenoses are very severe [1, 2]. Based on the process responsible for stress-induced ischemia, reduction of coronary flow reserve, myocardial perfusion abnormalities, and regional myocardial dysfunction are thought to be specific markers of ischemia [3, 4].

Semi-quantitative dobutamine stress echocardiography (Semi-DSE) has been used to detect CAD based on the fact that wall motion abnormalities develop during dobutamine stress in relation to the severity of the
coronary artery stenosis [5-9]. However, high doses of dobutamine are necessary to detect CAD even in patients with critical coronary stenosis. Furthermore, it is difficult to evaluate wall motion abnormalities during Semi-DSE in some patients including the issue of inter- and intra-observer variability. From a clinical point of view, Semi-DSE combined with coronary flow velocity and myocardial perfusion analysis might contribute to the evaluation of CAD. Measurement of coronary flow velocity (CFV) by transthoracic Doppler echocardiography (TTDE) during contrast-enhanced dobutamine stress can allow for the detection of stress-induced myocardial ischemia [10, 11]. Recently, experimental and clinical studies have shown that dobutamine stress myocardial contrast echocardiography (MCE) can detect myocardial perfusion abnormalities prior to the development of wall motion abnormalities [12, 13, 14].

We hypothesized that low-dose dobutamine stress with CFV and myocardial perfusion analysis could detect myocardial ischemia preceding the development of wall motion abnormalities and evaluate the grade of left anterior descending coronary artery (LAD) stenosis in patients with suspected CAD.

Methods

Study Population

The study population consisted of 96 patients out of 326 patients who underwent DSE study because of suspected CAD based on their history and the exercise electrocardiogram at Nippon Medical School Hospital during the period from November 2001 to December 2002. Patients were scheduled for Semi-DSE, MCE, and TTDE studies before elective coronary angiography (CAG). Exclusion criteria included the presence of myocardial infarction, unstable angina, tachyarrhythmia, second- or third-degree atrioventricular block, or use of β blockers. All patients gave informed consent.

Coronary Angiography

CAG was performed within 2 weeks of the other studies according to standard procedures using the femoral approach. Coronary stenosis is expressed as the percent reduction of the luminal diameter.

Semi-quantitative Dobutamine Stress Echocardiography

Two experienced echocardiographers, who were unaware of the clinical history, the exercise electrocardiogram, or results of CAG, performed the DSE, MCE, and TTDE studies. Dobutamine was infused intravenously at a dose of 5 μg·kg⁻¹·min⁻¹, and increased by 5-10 μg·kg⁻¹·min⁻¹ every 3 minutes up to a maximal dose of 40 μg·kg⁻¹·min⁻¹ with the addition of 0.5 mg of atropine if necessary. Transthoracic echocardiography was performed with a commercial instrument (Vivid ViVe; GE Vingmed, Horten, Norway) and a 2.5 MHz transducer. Standard echocardiographic images were obtained digitally. Eight segments (basal anterior, basal anterior septal, mid anterior, mid anterior septal, and 4 apical) were assigned to the LAD territory. Segmental wall motion was scored qualitatively using the quad screen cineloop format as follows: -1 = hyperkinetic, 0 = normal, 1 = mildly hypokinetic, 2 = severely hypokinetic, 3 = akinetic, 4 = dyskinetic. The patterns of segmental response to dobutamine were defined [15] as: biphasic (improvement in the wall motion score ≥1 grade during the low-dose dobutamine study followed by deterioration during the high-dose dobutamine study), worsening (deterioration of wall motion during dobutamine infusion), no change (absence of improvement or worsening during dobutamine infusion), sustained improvement (improvement without deterioration of wall motion from low to peak dose of dobutamine). The DSE was considered positive when segments showed biphasic or worsening patterns in the segmental response to dobutamine in all segments of the left ventricle. The results of semi-quantitative DSE (Semi-DSE) are expressed as follows: the extent of ischemia was indexed as the number of segments with biphasic or worsening patterns (SEG), and the severity of ischemia (SI) was indexed as the sum of the differences in wall-motion scores between peak stress and rest divided by the number of affected segments. If SEG was zero, SI was defined as zero. The images were analyzed by two observers who were unaware of patient clinical data, angiographic findings, or other echocardiographic results.

Transthoracic Doppler Echocardiography

Contrast-enhanced TTDE was performed immediately after MCE acquisition at baseline and at a dose of 10 μg·kg⁻¹·min⁻¹. The transducer was placed in the fourth intercostal space and rotated to get an appropriate color flow image of the distal portion of the LAD during Doppler color flow mapping as previously described [10, 16, 17]. The direction of the ultrasound beam was placed parallel to LAD flow. We recorded three consecutive coronary flow velocity signals and stored them in the ultrasound system. Two experi-
enced investigators measured the mean velocity of the diastolic Doppler velocity signals at baseline and during low-dose dobutamine stress. The coronary flow velocity ratio (CFV ratio) was calculated as follows: the ratio of the mean diastolic Doppler velocity during low-dose dobutamine stress divided by the mean diastolic Doppler velocity at baseline. The physicians who evaluated the DSE, MCE, and TTDE were blinded to the clinical history, the exercise electrocardiogram, and the results of CAG.

**Myocardial Contrast Echocardiography**

The ultrasound contrast agent, Levovist (Schering AG, Germany; 2.5 g diluted in 7 ml of sterile water) was infused continuously at a rate of 2.5 ml·min⁻¹ intravenously. MCE was performed at baseline and during low-dose dobutamine stress (10 µg·kg⁻¹·min⁻¹) in the harmonic power Doppler mode. We used a 2.5 MHz probe (1.67 MHz transmit/3.33 MHz receive). The machine settings included a mechanical index of 1.5, maximal dynamic range, and flat time gain compensation settings. End-systolic triggered images were obtained at increasing pulsing intervals during continuous infusion of Levovist. The pulsing interval was increased from every heart beat to every 2, 3, 4, 6, 8, 10, and 12 cardiac cycles. All images acquired in the apical 4- and 2-chamber views were digitally stored.

MCE images were analyzed qualitatively and quantitatively. Qualitative analysis was accomplished as five segments including the apex, apical septum, apical anterior, mid anterior, and basal anterior in the territory of the LAD were analyzed in the apical 4- and 2-chamber views. End-systolic triggering was used and myocardial perfusion was graded as absent, patchy, or full. The patterns of change in myocardial perfusion during low-dose dobutamine stress were defined as follows: full (full or improved opacification), worsening (any deterioration of myocardial opacification), or no change (persistence of patchy myocardial opacification). Images were evaluated by two observers blinded to the clinical data and coronary anatomy.

For the quantitative analysis, appropriate MCE images in aligned frames from different pulse intervals were chosen and analyzed off-line. The average pixel intensity was measured in regions of interest that were drawn over the mid myocardium on end-systolic frames. The relationship between the pulse intervals and background subtracted myocardial video-intensity measurements was analyzed and fitted to the exponential function, \( y = A \left(1 - e^{-\beta t}\right) \), where \( y \) is the video-intensity at a various pulse intervals of \( t \), and \( A \) is the peak plateau amplitude. Video-intensity represents myocardial blood volume, and \( \beta \) is the rate of signal intensity rise that represents the mean microbubble velocity [18, 19]. The A ratio and \( \beta \) ratio were calculated as follows: the ratio of \( A \) and \( \beta \) during low-dose dobutamine stress divided by \( A \) and \( \beta \) at baseline, respectively.

**Statistical Analysis**

Univariate analysis of categorical variables was performed with the \( \chi^2 \) test and Fisher’s exact test, and continuous variables were analyzed by Student’s t-test. Correlations among parameters were evaluated by linear regression analysis. Differences were considered significant at P<0.05. Receiver operating characteristics (ROC) curves were used to determine the optimal cut-off point and compare the efficacy of diagnostic tests (the Somer’s D statistic). Statistical analysis was performed using SPSS software (10.0, SPSS Inc).

**Results**

**Patient Characteristics**

All studies were carried out successfully in 85 out of 96 patients who were suspected of angina pectoris clinically. The remaining eleven patients were excluded because of poor recordings, and the feasibility of recording the CFV and the MCE in all patients was 93% and 96%, respectively. Thirty-eight patients (45%) were in Canadian Cardiovascular Society (CCS) class I, and 47 (55%) were in CCS class II. With respect to cardiac medication use, 68% of patients were on calcium antagonists, 54% on nitrates, and 100% on aspirin. Of 85 patients, coronary angiography revealed normal coronary arteries in 28 patients, CAD without LAD lesion in 29, patients and CAD with LAD lesion in 28 patients (a 75% LAD stenosis was present in 10 patients and a ≥90% LAD stenosis was present in 18 patients). In 28 patients with LAD lesions, 16 patients had single vessel disease, and there was only 1 patient with evidence of collateral circulation (right to left). In the remaining 29 patients, coronary angiography revealed a ≥75% right coronary artery stenosis and/or a ≥75% circumflex coronary artery stenosis without LAD lesions. Age, gender, history, left ventricular ejection fraction at baseline, heart rate, and rate-pressure product during low-dose dobutamine stress did not differ statistically between patients with CAD and patients who did not have CAD (Table 1).

There were significant differences in the maximum dose of dobutamine, the rate-pressure product, SEG,
and SI between the patients with CAD and the patients with normal coronary arteries (P<0.001, Table 1). However, SEG and SI were zero in 85 patients during low-dose dobutamine stress.

**Semi-DSE**

In all patients, the sensitivity and specificity of semi-DSE (SEG and SI) for detecting ≥75% LAD stenosis were 79% and 85% and 93% and 77%, respectively. The optimal cut-off value for detecting ≥75% LAD stenosis based on semi-DSE data was defined by ROC curve analysis as a value of 2.5 for SEG and a value of 0.7 for SI (Figure 1, Table 2). The area under the curve of SEG was better than that of SI.

**Coronary Flow Velocity and CFV Ratio Using Ultrasonic Contrast Agent**

Table 2 shows that the CFV ratio using ultrasonic contrast agent could identify patients with ≥75% stenosis with a sensitivity and specificity of 100% and 89%, respectively, and the best cut-off value for differentiating normal patients from patients with ≥75% LAD stenosis was defined by ROC curve analysis as a value of 1.81 for CFV ratio.

**Changing Patterns of Myocardial Contrast Perfusion during Low-dose DSE**

Figure 2 demonstrates that all 18 regions supplied by the LAD with ≥90% stenosis showed worsening or no change pattern of myocardial opacification and 57 regions supplied by a normal LAD were fully or improvingly opacified. However, in 10 regions supplied by the LAD with 75% stenosis, 5 regions showed worsening or no change pattern; the other 5 had improving or full opacification.

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**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Patients with CAD (with LAD lesion)</th>
<th>Patients with CAD (without LAD lesion)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>67 ± 8</td>
<td>69 ± 8</td>
<td>70 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>16/12</td>
<td>18/10</td>
<td>16/13</td>
<td>NS</td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HT</td>
<td>20 (71)</td>
<td>19 (69)</td>
<td>22 (75)</td>
<td>NS</td>
</tr>
<tr>
<td>DM</td>
<td>6 (21)</td>
<td>8 (29)</td>
<td>8 (30)</td>
<td>NS</td>
</tr>
<tr>
<td>HL</td>
<td>8 (28)</td>
<td>8 (30)</td>
<td>10 (34)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>11 (39)</td>
<td>14 (50)</td>
<td>12 (41)</td>
<td>NS</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>67 ± 5</td>
<td>62 ± 9</td>
<td>65 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>DSE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at rest: HR (beat·min⁻¹)</td>
<td>71 ± 11</td>
<td>68 ± 13</td>
<td>66 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>systolic BP (mmHg)</td>
<td>134 ± 22</td>
<td>142 ± 26</td>
<td>136 ± 28</td>
<td>NS</td>
</tr>
<tr>
<td>at low-dose DOB stress</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beat·min⁻¹)</td>
<td>88 ± 17</td>
<td>80 ± 8</td>
<td>79 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>RPP (mmHg·beat⁻¹·min⁻¹)</td>
<td>10890 ± 2815</td>
<td>13246 ± 2432</td>
<td>11098 ± 1890</td>
<td>NS</td>
</tr>
<tr>
<td>SEG</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>SI</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>at peak dose of DOB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>peak dose (µg·kg⁻¹·min⁻¹)</td>
<td>40 ± 0</td>
<td>32 ± 8*</td>
<td>34 ± 6*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RPP (mmHg·beat⁻¹·min⁻¹)</td>
<td>20,663 ± 1,812</td>
<td>15,460 ± 1,766*</td>
<td>17,288 ± 1,856*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SEG</td>
<td>1.3 ± 1.9</td>
<td>4.9 ± 2.3*</td>
<td>4.6 ± 2.5*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SI</td>
<td>0.2 ± 0.4</td>
<td>0.9 ± 0.4*</td>
<td>0.8 ± 0.3*</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; DM, diabetes mellitus; DSE, dobutamine stress echocardiography; HL, hyperlipidemia; HT, hypertension; LAD, left anterior descending coronary artery; LVEF, left ventricular ejection fraction; HR, heart rate; BP, blood pressure; DOB, dobutamine; RPP, rate pressure product.

SEG, number of segments exhibiting deteriorating wall motion during stress SI, summation of the difference of the scores (wall motion score at peak stress minus wall motion score at rest) divided by the number of segments exhibiting deteriorating wall motion at the peak stress. Continuous values are reported as the mean ± SD. ( ), %.

*control patients versus patients with LAD lesions and patients without LAD lesions.
Quantitative Analysis of Myocardial Contrast Perfusion

At baseline or during low-dose dobutamine stress, the sensitivity and the specificity of the peak plateau video-intensity (A) and the bubble velocity (β) for detecting patients with ≥75% LAD stenosis were lower (Table 2). However, the sensitivity and the specificity of the A ratio and β ratio were 85% and 92% and 72% and 68%, respectively, in patients with ≥75% LAD stenosis. The best cut-off value for identifying patients with ≥75% LAD stenosis was defined by ROC curve analysis as a value of 1.06 for the A ratio and a value of 1.23 for the β ratio. There were good correlations between the indices of quantitative analysis for MCE (A ratio and β ratio) and the CFV ratio (Figure 3).

Diagnostic Index Values of Each Method for Detecting Left Anterior Coronary Artery Disease

Using the Somer’s D statistic, differences in area under the curve of SEG from the CFV ratio, the MCE A ratio, and the MCE β ratio are shown in Table 2.

![Sensitivity and specificity of Semi-DSE for detecting ≥75% LAD stenosis.](image)

CAG= coronary angiography; DSE= dobutamine stress echocardiography; LAD= left anterior descending coronary artery

**Table 2.** Diagnostic index of each method for detecting ≥75% coronary stenosis in the left anterior coronary artery.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Cut-off value</th>
<th>AUC</th>
<th>95% CI</th>
<th>Somer’s D</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semi-DSE SEG</td>
<td>79</td>
<td>93</td>
<td>2.5</td>
<td>0.898</td>
<td>0.816 – 0.980</td>
<td>-0.399</td>
<td>0.005</td>
</tr>
<tr>
<td>SI</td>
<td>85</td>
<td>77*</td>
<td>0.7</td>
<td>0.83</td>
<td>0.737 – 0.923</td>
<td>-0.328</td>
<td>0.01</td>
</tr>
<tr>
<td>CFV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>75</td>
<td>65*</td>
<td>18.5</td>
<td>0.755</td>
<td>0.619 – 0.891</td>
<td>-0.328</td>
<td>0.01</td>
</tr>
<tr>
<td>DOB stress</td>
<td>96</td>
<td>93</td>
<td>36.5</td>
<td>0.964</td>
<td>0.916 – 1.012</td>
<td>-0.560</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ratio</td>
<td>100**</td>
<td>89</td>
<td>1.81</td>
<td>0.973</td>
<td>0.937 – 1.009</td>
<td>-0.600</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MCE A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>54</td>
<td>53*</td>
<td>34.3</td>
<td>0.423</td>
<td>0.248 – 0.598</td>
<td>0.102</td>
<td>0.417</td>
</tr>
<tr>
<td>DOB stress</td>
<td>69</td>
<td>58*</td>
<td>40.5</td>
<td>0.705</td>
<td>0.523 – 0.887</td>
<td>0.221</td>
<td>0.083</td>
</tr>
<tr>
<td>Ratio</td>
<td>85</td>
<td>72*</td>
<td>1.06</td>
<td>0.845</td>
<td>0.722 – 0.967</td>
<td>-0.413</td>
<td>0.007</td>
</tr>
<tr>
<td>MCE β</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>46</td>
<td>40*</td>
<td>0.31</td>
<td>0.345</td>
<td>0.170 – 0.520</td>
<td>0.102</td>
<td>0.212</td>
</tr>
<tr>
<td>DOB stress</td>
<td>77</td>
<td>61*</td>
<td>0.41</td>
<td>0.74</td>
<td>0.587 – 0.894</td>
<td>-0.324</td>
<td>0.394</td>
</tr>
<tr>
<td>Ratio</td>
<td>92</td>
<td>68*</td>
<td>1.23</td>
<td>0.853</td>
<td>0.739 – 0.967</td>
<td>-0.545</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AUC, area under the curve; CFV, coronary flow reserve; MCE, myocardial contrast echocardiography

*p<0.01, **p<0.05.  Semi-DSE (SEG) versus CFV, MCE-A, and MCE-β
The diagnostic efficacies of the CFV ratio, the MCE A ratio, and the MCE β ratio are significantly different from each other. The efficacy of CFV ratio was superior to that of other indices.

Utility of Combined Assessment of CFV Ratio and Myocardial Perfusion

Semi-DSE study showed 22 true positive and 6 false negative findings in 28 patients with ≥75% LAD stenosis, and in the remaining 57 patients, 4 false positive findings in the LAD territory. In 22 true positive and 3 out of 6 false negative cases, failures of the CFV ratio and β ratio to increase >1.81 and >1.23 times that at
baseline indicate the presence of ≥75% LAD stenosis. The remaining 3 of the 6 false negative cases had multivessel disease (Figure 4).

In 26 patients with a positive Semi-DSE, all 18 patients with ≥90% LAD stenosis had a CFV ratio ≤ 1.81 and a β ratio ≤1.23. However, half of the patients with 75% LAD stenosis had a CFV ratio ≤1.81 and a β ratio >1.23 (Figure 5).

Discussion

This study demonstrates that low-dose dobutamine stress combined with coronary flow velocity and myocardial perfusion can detect critical LAD stenosis preceding wall motion abnormalities. Specifically, the CFV ratio is a useful method because it can be calculated during stress, and the CFV ratio showed a good correlation with the A ratio and β ratio of MCE. A CFV ratio ≤1.81 and a β ratio ≤1.23 were able to identify patients with critical LAD stenosis.

Ischemic cascade

The ischemic cascade has been demonstrated by experimental and clinical studies [13, 20, 21]. It is a temporal sequence of events beginning with reduced regional myocardial perfusion, metabolic and biochemical changes, left ventricular diastolic dysfunction, impaired left ventricular systolic function, electrocardiographic abnormalities with ST segment alterations, and anginal symptoms. Dobutamine induces an imbalance between myocardial oxygen supply and demand followed by the ischemic cascade. DSE has been established as one of the useful tools for detecting CAD [5-9]. However, in DSE studies, use of high-dose dobutamine with additional injections of atropine impaired the ability to evaluate wall motion, and prolonged testing are limitations. Based on the ischemic cascade, the reduction in coronary flow reserve and the abnormal regional myocardial perfusion would be expected to be evaluated by TTDE and MCE even during low-dose dobutamine infusion.

Semi-DSE

Although SEG and SI can be used to detect ≥75% LAD stenosis, SEG was more accurate than SI for detecting ≥75% LAD stenosis based on the Somer’s D statistic. As one of the semi-DSE indices, SEG was used to analyze the diagnostic efficacies of semi-DSE versus CFV and MCE in this study. Semi-DSE showed 6 false negative and 4 false positive cases in the study patients. Five of the six false negative cases had multivessel disease, including left anterior descending coronary artery disease. In the setting of multivessel disease, a wall motion abnormality in the LAD territory might be masked if the severity of stenosis in other coronary arteries is greater than that in the LAD.

CFV ratio during DSE

Contrast-enhanced transthoracic second harmonic Doppler echocardiography can be carried out usually in combination with adenosine infusion [22]. Previous studies have shown that CFV in the distal LAD can be measured by contrast-enhanced TTDE during dobutamine stress, and changes in the CFV are correlated with stress induced wall motion abnormalities and the degree of coronary stenoses [10, 11]. However, in our experience, it is relatively difficult to evaluate CFV during high-dose dobutamine because of augmentation of heart contractions. Therefore, we performed TTDE in combination with only low-dose dobutamine stress. The CFV ratio can be calculated during dobutamine stress, and this information might be helpful in making clinical decisions. Vatner SF [23] showed that significant impairment of myocardial function was induced by only 10~20% reductions in blood flow and that greater degree of flow reduction caused greater severity in wall motion abnormality in experiments. Ahmari SAL et al. [24] have shown that patients with developing abnormal wall thickening demonstrated significantly lower coronary flow velocity ratio at low dose, as well as at peak dobutamine dose compared to patients with normal wall thickening. These data are similar to those presented here.

MCE during DSE

MCE has been shown to quantify myocardial blood flow velocity noninvasively in experimental studies [18]. MCE is based on the microvascular rheology of microbubbles that is similar to that of red blood cells. Wei et al. [25] and Jayaweera et al. [26] have shown that the magnitude of a myocardial perfusion defect in a clinical study following the administration of adenosine is related to the severity of coronary stenoses. A recent study has demonstrated that the sensitivity of myocardial contrast perfusion abnormalities is greater than that of wall motion abnormalities for the detection of coronary stenosis > 50% diameter, even at a low dose of dobutamine infusion [13]. Few clinical studies have quantified myocardial perfusion, coronary flow velocity, and myocardial contractility simultaneously using contrast-enhanced DSE. In this study, myocardial perfusion and coronary flow velocity ratio were evaluated at rest and during low-dose dobutamine stress with
contrast enhancement followed by a standard titration protocol for DSE. Quantitative analysis of MCE was performed using an off-line computer. MCE data were fitted to Wei’s exponential function: $y = A (1 - e^{-\beta \cdot t})$. Previous studies showed that the $\beta$ ratio has advantages to and is more accurate than the A ratio for detecting coronary stenosis in the clinical setting [13, 18]. We demonstrated that there is a good correlation between the $\beta$ ratio and the CFV ratio, and the best cut-off values for the presence of $\geq 75\%$ LAD stenosis, 1.23 for the $\beta$ ratio and 1.81 for the CFV ratio during low-dose dobutamine stress, reduced false positive results in this study.

Limitations

There are some methodological limitations. First, we could not measure the entire envelope of coronary flow without the use of a contrast agent. The contrast agent produces bubble noise when it aggregates just after injection. Therefore, in some cases it was necessary to adjust the transmission power. Second, we attempted to maintain the same echocardiographic view, Doppler angle, and depth of sample point to obtain a complete diastolic Doppler envelope. However, we could not obtain complete data in 10% of patients. From a clinical point of view, the feasibility of those tests should be evaluated carefully. Third, both TTDE and CFV were only applied to the analysis of the LAD territory. The application of other coronary territories still remains to be tested. Therefore, the multivessel cases could not be evaluated in this study. Fourth, in multivessel disease, it is not necessary that myocardial perfusion, CFV, and contractility deteriorate first in LAD territory. In this study, five out of the 6 false negative studies were in patients with multivessel disease, and three of those patients had normal perfusion and CFV ratio in the LAD bed. Fifth, the acquisition of MCE data is time consuming, and those data are not available during the DSE study.

Clinical Implications

Semi-DSE combined with the newly developed TTDE and MCE has the potential for overcoming the limitations of Semi-DSE alone. When the CFV ratio and myocardial perfusion abnormalities are detected during low-dose dobutamine stress, it may be possible to stop the DSE study and make clinical decisions without any additional stress. In case that those abnormalities are uncertain, the DSE study should be continued. In some false positive and negative cases with Semi-DSE, such as in the setting of LBBB, new cut-off values of the CFV ratio and MCE could reduce those cases.

Conclusion

This study demonstrated that the CFV ratio during low-dose dobutamine stress correlates well with the $\beta$ ratio, which represents the microbubble velocity, and the combined use of TTDE and MCE during low-dose dobutamine stress can succeed in detecting LAD lesions more accurately than Semi-DSE alone.

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References


