Noninvasive Assessment of Significant Left Anterior Descending Coronary Artery Stenosis by Coronary Flow Velocity Reserve With Transthoracic Color Doppler Echocardiography

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Background—Coronary flow reserve has been considered an important diagnostic index of the functional significance of coronary artery stenosis. With Doppler technique, it has been assessed as the ratio of hyperemic to basal coronary flow velocity (coronary flow velocity reserve [CFVR]) by invasive or semiinvasive methods with a Doppler catheter, a Doppler guide wire, and a transesophageal Doppler echocardiographic probe. Recent technological advancement in transthoracic Doppler echocardiography (TTDE) provides measurement of coronary flow velocity in the distal portion of the left anterior descending coronary artery (LAD) and may be useful in the noninvasive CFVR measurement. The purpose of this study was to evaluate the value of CFVR determined by TTDE for the assessment of significant LAD stenosis.

Methods and Results—We studied 36 patients who underwent coronary angiography for the assessment of coronary artery disease. The study population consisted of 12 patients with significant LAD stenosis (group A) and 24 patients without significant LAD stenosis (group B). With TTDE, coronary flow velocities in the distal LAD were recorded at rest and during hyperemia induced by intravenous infusion of adenosine (0.14 mg • kg⁻¹ • min⁻¹) under the guidance of color Doppler flow mapping. Adequate spectral Doppler recordings of coronary flow in the distal LAD for the assessment of CFVR were obtained in 34 of 36 study patients (94%). The peak and mean diastolic coronary flow velocities at baseline did not differ between groups A and B (23.6±10.3 versus 22.9±6.6 cm/s and 16.4±8.6 versus 14.5±4.0 cm/s, respectively). However, the peak and mean coronary flow velocities during hyperemia in group A were significantly smaller than those in group B (35.6±16.3 versus 54.2±16.3 cm/s and 24.7±13.1 versus 37.9±13.0 cm/s, respectively; P<.01). There were significant differences in CFVR obtained from peak and mean diastolic velocity between groups A and B (1.5±0.2 versus 2.4±0.4 and 1.5±0.2 versus 2.6±0.4, respectively; P<.001). A CFVR from peak diastolic velocity <2.0 had a sensitivity of 92% and a specificity of 82% for the presence of significant LAD stenosis. A CFVR from mean diastolic velocity <2.0 had a sensitivity of 92% and a specificity of 86% for the presence of significant LAD stenosis.

Conclusions—CFVR determined by TTDE is useful in the noninvasive assessment of significant stenotic lesion in the LAD. (Circulation. 1998;97:1557-1562.)

Key Words: blood flow • coronary disease • echocardiography

Coronary flow reserve estimated by drug-induced coronary vasodilation has been considered an important diagnostic index of functional significant coronary artery stenosis.1-6 With Doppler technique, it has been alternatively assessed as the ratio of hyperemic to basal coronary flow velocity (CFVR) after angiographically induced coronary vasodilation by invasive techniques with a Doppler catheter7-12 or a Doppler guide wire.13-20 Although these methods have already been established as useful techniques, they are available only during cardiac catheterization and limit the clinical application of CFVR in the assessment of coronary artery disease. Recent several reports have shown that CFVR measured by transesophageal Doppler echocardiography is useful in the assessment of significant LAD stenosis.21-23 However, the transesophageal approach is not noninvasive but semiinvasive.

Several studies have reported that the epicardial coronary blood flow velocity can be measured by TTDE, which is noninvasive and widely used in the clinical setting.24-28 To the best of our knowledge, however, no report has evaluated the usefulness of CFVR measured by this noninvasive method. Recent technological advancement in color Doppler echocardiography may provide high success rate in measuring coronary flow velocity and noninvasive CFVR assessment. The purpose of this study was to evaluate the value of CFVR determined by TTDE for the assessment of significant LAD stenosis.
Methods

Study Patients
We prospectively examined 36 consecutive patients (27 men, 9 women; mean age, 59±15 years) who underwent coronary angiography for the evaluation of coronary artery disease. Patients with unstable angina, decompensative congestive heart failure, atrial fibrillation, previous coronary bypass graft surgery, diabetes mellitus, severe chronic obstructive pulmonary disease, or bronchospasm were not enrolled. None had a clinical history or ECG signs of a previous myocardial infarction, history of systemic hypertension, or evidence of primary myocardial or valvular heart disease. No patient had evidence of LV hypertrophy (septal or posterior wall thickness at diastole >12 mm) on echocardiographic examination. Reason for coronary angiography was evaluation for coronary artery disease. Of the 36 patients, 12 had a significant stenotic lesion in the proximal or middle portion of the LAD (group A; diameter stenosis >70%; 9 men, 3 women; mean age, 69±6 years); the remainder did not have a significant stenotic lesion in the LAD (group B; 18 men, 6 women; mean age, 54±15 years). In all the study patients, there was no significant stenosis (diameter stenosis >70%) in the other coronary arteries besides the LAD. All participants gave informed consent to the protocol approved by the Committee for the Protection of Human Subjects in Research at Kobe General Hospital.

Doppler Echocardiographic Studies
Echocardiographic examinations were performed with an ATL HDI-3000CV digital ultrasound system with a frequency of 4 to 7 MHz (Doppler frequency, 4 MHz; Advanced Technology Laboratory), and a Toshiba SSA-380A digital ultrasound system with a frequency of 7.5 MHz (Doppler frequency, 5 MHz). In color Doppler flow mapping, velocity range was set at ±24.0 or ±19.2 cm/s in the ATL system and ±17.4 or ±16.1 cm/s in the Toshiba system. The color gain was adjusted to provide optimal images. The acoustic window was around the midclavicular line in the fourth and fifth intercostal spaces in the left lateral decubitus position. The ultrasound beam was transmitted toward the heart to visualize coronary blood flow in the LAD by color Doppler echocardiography (Fig 1). First, the left ventricle was imaged in the long-axis cross section, and then the ultrasound beam was inclined laterally. Next, coronary blood flow in the distal portion of the LAD was searched under the guidance of color Doppler flow mapping (Fig 2). With a sample volume (1.5 or 2.0 mm wide) positioned on the color signal in the LAD, Doppler spectral tracings of flow velocity in the LAD were recorded by fast Fourier transformation analysis (Fig 3). The spectral Doppler of the LAD flow showed a characteristic biphasic flow pattern with a larger diastolic component and a small systolic one. All studies were continuously recorded on 1/2 inch super-VHS videotape for off-line analysis.

CFVR Measurements by TTDE
We first recorded baseline spectral Doppler signals in the distal portion of the LAD. Adenosine was administered (140 μg·kg⁻¹·min⁻¹ IV) for 2 minutes to record spectral Doppler signals during hyperemic conditions. All patients had continuous heart rate and ECG monitoring. Blood pressure was recorded at baseline, every minute during adenosine infusion, and at recovery.

Each study was analyzed by one experienced investigator who was unaware of the other patient data. Measurements were performed off-line by tracing the contour of the spectral Doppler signal using the computer incorporated in the ultrasonic system. MDV and PDV were measured at baseline and peak hyperemic conditions. An average of the measurements was obtained in three cardiac cycles. CFVR was defined as the ratio of hyperemic to basal peak diastolic coronary flow velocity (CFVR PDV) and the ratio of hyperemic to basal mean diastolic coronary flow velocity (CFVR MDV). Normal CFVR was defined as >2.0 on the basis of previous studies that evaluated flow velocities in the distal LAD.

Two-dimensional Echocardiographic Measurements of LV Function at Baseline
Before CFVR measurements by TTDE, we measured LV wall (septal and posterior wall thickness) at end diastole by two-dimensional echocardiography. LV volume measurements were performed according to the recommendation of the American Society of Echocardiography. Apical two- and four-chamber views were obtained at baseline. End-diastolic and end-systolic LV volumes were computed by use of modified Simpson's method (method of disks). When only one apical view was of adequate quality for assessment, modified Simpson's method was used in either the four- or two-chamber view to calculate LV volumes. Ejection fraction was calculated as follows: (end-diastolic LV volume—end-systolic LV volume)/(end-diastolic LV volume)×100. Furthermore, we assessed regional wall motion at rest on the basis of 16 segments of the LV as recommended by the American Society of Echocardiography.

Coronary Angiography
Coronary angiography was performed by the Judkins technique after injection of 4000 IU IV heparin. Coronary stenosis was evaluated by use of multiple projections by an experienced investigator unaware of the echocardiographic data. Quantitative analysis was done with a MEDIS (Medical Imaging Systems CMS analysis software). A stenosis was considered significant if there was >70% lumen diameter narrowing in at least one projection.

Data Analysis
Mean and SD are expressed for the parametric data. The differences between the two groups for the parametric data were tested by use of an unpaired two-tailed t test. Differences between baseline and hyperemic data within the two groups were tested by use of a paired two-tailed Student's t test. Sensitivity, specificity, positive predictive...
value, and negative predictive value for CFVR as a predictor of significant LAD stenosis were calculated in the traditional manner. Interobserver and intraobserver variabilities were assessed for velocity measurements in 15 recordings in seven randomly selected patients. Interobserver variability was calculated as the SD of the differences between the measurements of two independent observers who were unaware of the other patient data and expressed as a percent of the average value. Intraobserver variability was calculated as the SD of the differences between the first and second determination (3-week interval) for a single observer and expressed as a percent of the average value.

Results
Under the guidance of color Doppler flow mapping, adequate spectral Doppler recordings of coronary flow in the distal portion of the LAD for the assessment of CFVR were obtained 34 of 36 study patients (94%). No patient noted AV block, chest pain, flushing, or palpitations during the vasodilator infusion in the TTDE studies.

LV Function at Baseline
For the measurement of LV wall thickness (septal and posterior wall), there were no significant differences between groups A and B (9.7±1.2 versus 9.8±1.4 mm and 10.0±1.0 versus 9.9±1.1 mm, respectively). Both end-diastolic and end-systolic LV volumes did not differ between groups A and B (93.4±10.9 versus 97.2±6.6 mL and 36.9±10.2 versus 40.3±6.0 mL, respectively) at baseline. There was no significant difference in ejection fraction measurement between groups A and B (60.9±6.9% versus 58.7±4.7%). In each case in both groups, segmental wall motion abnormality was not found by two-dimensional echocardiography at baseline.

Hemodynamics
During drug administration, heart rate increased from 68±10 to 78±12 bpm (P<.001) in the study patients. Systolic arterial pressure decreased from 120±12 to 110±10 mm Hg.
CFVR in Patients With and Without Significant LAD Stenosis

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Baseline</th>
<th>Hyperemia</th>
<th>CFVR PDV</th>
<th>Baseline</th>
<th>Hyperemia</th>
<th>CFVR MDV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (&gt;70% LAD stenosis)</td>
<td>23.6±10.3</td>
<td>35.6±16.3*</td>
<td>1.5±0.2†</td>
<td>16.4±8.5</td>
<td>24.7±13.1*</td>
<td>1.5±0.2†</td>
</tr>
<tr>
<td>Group B (&lt;70% LAD stenosis)</td>
<td>22.9±6.6</td>
<td>54.2±16.3</td>
<td>2.4±0.4</td>
<td>14.5±4.0</td>
<td>37.9±13.0</td>
<td>2.6±0.4</td>
</tr>
</tbody>
</table>

*P<.01 vs group B; †P<.001 vs group B.

(P<.05), and diastolic arterial pressure decreased from 72±10 to 60±6 mm Hg (P<.001). An increase in coronary flow velocity was obtained within 50 seconds of the start of the vasodilator infusion. Flow velocity remained stable throughout the infusion period and returned to baseline within 30 seconds of discontinuation of the drug.

**CFVR Measurement by TTDE**

PDV and MDV at baseline did not differ between groups A and B (23.6±10.3 versus 22.9±6.6 cm/s and 16.4±8.6 versus 14.5±4.0 cm/s, respectively; see the Table). However, PDV and MDV during hyperemia in group A were significantly smaller than those in group B (35.6±16.3 versus 54.2±6.3 cm/s and 24.7±13.1 versus 37.9±13.0 cm/s, respectively; P<.01; the Table). There were significant differences in CFVR PDV and CFVR MDV measured in groups A and B (1.5±0.2 versus 2.4±0.4 and 1.5±0.2 versus 2.6±0.4, respectively; P<.001; the Table and Figs 4 and 5). A CFVR (PDV) < 2.0 had a sensitivity of 92%, a specificity of 82%, positive predictive value of 73%, and a negative predictive value of 95% for the presence of significant LAD stenosis (Fig 6). A CFVR MDV < 2.0 had a sensitivity of 92%, a specificity of 86%, positive predictive value of 79%, and a negative predictive value of 95% for the presence of significant LAD stenosis (Fig 7).

**Observer Variabilities**

Interobserver and intraobserver variabilities for the measurements of Doppler velocity recordings were 4.8% and 4.0%, respectively.

**Discussion**

In the present study, we evaluated the value of CFVR determined by TTDE for the assessment of significant LAD stenosis after drug-induced coronary vasodilation. TTDE was shown to be a feasible method for the noninvasive measurement of CFVR and detection of significant LAD stenosis.

**CFVR Measurements by Conventional Methods**

It has been reported that assessment of coronary flow reserve by administration of coronary vasodilators provides an important diagnostic index of the functional significant coronary artery stenosis.1-4 With Doppler technique, coronary flow reserve has been alternatively assessed as the ratio of hyperemic to basal coronary flow velocity after drug-induced coronary vasodilation by invasive techniques with a Doppler catheter2-4 or a Doppler guide wire5-10 because changes in coronary flow velocities induced by coronary vasodilatation closely reflect changes in coronary blood flow.7 Although these invasive methods have already been established as useful techniques, they are available only in the catheterization laboratories and limit the clinical application of CFVR in the assessment of coronary artery disease. Positron emission tomography has been used to measure coronary flow reserve noninvasively.33 However, this method is expensive and not generally available. Several studies have reported that transesophageal Doppler echocardiography is useful in the assessment of significant LAD stenosis by measuring hyperemic to basal coronary flow velocity in the proximal LAD.21-23 However, strictly speaking, the transesophageal approach is not noninvasive, but semi-invasive.

TTDE is noninvasive, relatively inexpensive, and widely used in the clinical setting and can be used for serial studies in echocardiographic laboratories. Fusejima34 reported that it was possible to measure coronary flow velocity in the midportion of the LAD with two-dimensional Doppler echocardiography. However, the measurement of coronary flow velocity was possible in 35% of the normal subjects and 50% of the patients with cardiovascular disease because it was performed without the guidance of color Doppler flow mapping. Ross et al35 reported that coronary flow velocity in the distal LAD was
measured in 33% of the study patients, although the distal LAD was visualized with high-frequency (7.5 MHz), two-dimensional ultrasound in 85% of the study patients. In their study, color Doppler flow mapping was not used to detect coronary flow signal in the LAD. The success rate in the measurement of coronary flow velocity in the middle to distal LAD by the conventional transthoracic approach without the guidance of color Doppler flow mapping is not sufficient for the assessment of CFVR. Thus, there has been no report to date of evaluating CFVR by the transthoracic approach.

**CFVR Measurements by TTDE**

In the present study, the success rate of the measurement of coronary flow velocity in the distal LAD for the assessment of CFVR was much higher (94%) compared with the previous reports using conventional TTDE. The high success rate in this study was due to the following reasons: reduction of the velocity range in color Doppler flow mapping and modified method to position the sample volume in the distal LAD under the guidance of color Doppler flow mapping. First, the reduction in the velocity range enhanced the visualization of the low-velocity signal in the distal LAD by lowering the cutoff limit of the wall motion filter. The velocity range in conventional color Doppler flow mapping is usually set in the range of ~60 to 70 cm/s in routine echocardiographic examinations. It is possible that use of conventional ultrasound systems that incorporate color Doppler flow mapping set only in the high velocity range leads to difficulty in visualization of the low-velocity signals usually seen in the LAD flow. In our present study, we lowered the setting of the velocity range in color Doppler flow mapping. Application of this newly modified velocity range in color Doppler flow mapping provided improved visualization of coronary flow signal in the distal LAD. Second, our method combined color Doppler flow mapping and the conventional pulsed Doppler technique. This modification facilitated the positioning of the sample volume in the distal LAD flow. Our study demonstrated that color Doppler flow mapping enables a more efficient guidance of the sample volume in the distal LAD compared with previous studies that used only two-dimensional imaging. Although the previous studies reported that successful detection of the middle to distal LAD flow was 33% to 50%, we were able to significantly improve the success rate to 94%. With the transesophageal approach, the success rate of the detection of coronary flow velocity in the proximal LAD has been reported to be from 69% to 89%. The success rate with the present transthoracic approach is higher than with the transesophageal studies. Furthermore, the transthoracic approach is completely noninvasive. The higher success rate in the assessment of CFVR and the fact that it is a noninvasive procedure should be important advantages in the present transthoracic method.

**Study Limitations**

We measured changes in coronary flow velocity, not changes in coronary blood flow. However, it has been reported that changes in coronary flow velocities induced by coronary vasodilation closely reflect changes in coronary blood flow. Previous studies with Doppler catheter, Doppler guide wire, and transesophageal Doppler echocardiography have shown that these techniques are useful in the prediction of significant coronary artery stenosis by the assessment of changes in coronary flow velocity. Second, we measured CFVR from only diastolic mean velocities, not mean velocities throughout the entire cardiac cycle. It was difficult to obtain complete Doppler spectral envelopes throughout the entire cardiac cycle because of cyclic cardiac motion in 6 of the 36 patients (17%). However, diastolic component of the spectral Doppler signal of the LAD flow could be clearly obtained by positioning the sample volume in the LAD during the diastolic phase under the guidance of color Doppler flow mapping in 34 of the 36 patients. In the previous studies using transesophageal Doppler echocardiography, the ratio of hyperemic to basal MDV and PDV was useful in the evaluation of functional coronary stenosis.

Third, in the present study, there was only a small number of patients with significant coronary stenosis in the LAD.
future investigations, more patients should be studied by the present method.

In the present study, we excluded several factors influencing CFVR measurement such as LV hypertrophy and myocardial infarction. However, other potential determinants of CFVR that were not measured and were not excluded in this study may affect the validity and specificity for the presence of significant LAD stenosis in the present method.

Finally, in the present study, only CFVR in the LAD was assessed by TTDE. Further investigation is necessary so that CFVR of the other coronary vessels can be assessed by this noninvasive method.

Conclusions
CFVR determined by TTDE is useful in the noninvasive assessment of significant LAD stenosis.

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References
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