Assessment of coronary flow velocity (CFV) and CFV reserve (CFVR) provides information about the functional significance of coronary artery stenosis and has been useful for determining the indication or end points of catheter-based coronary intervention (1–4). These measurements are usually obtained by sensor-tipped angioplasty Doppler guidewires, which are only applicable in the cardiac catheterization laboratory. Recent advances in transthoracic Doppler echocardiography (TTDE) make the measurement of CFV in the left anterior descending coronary artery (LAD) feasible with a high success rate. The CFVR in the distal LAD by TTDE has been assessed using vasodilators like adenosine and dipyridamole, and its clinical usefulness has been validated (5–10). We are not aware of any published studies that measured CFV response during dobutamine infusion by TTDE. This may be due to the inherent technical difficulty of measuring flow during augmented cardiac contraction. Intravenous transpulmonary contrast agents can improve detection of Doppler flow envelope by enhancing signal amplitude (5,6,10,11). We undertook this study to test the following hypotheses: 1) CFV in the LAD by TTDE can be adequately measured at baseline and during sequential doses of dobutamine infusion after transpulmonary contrast agent, and 2) there is good correlation between CFV measured by TTDE and stress-induced wall motion abnormality (WMA) in the LAD territory.

METHODS

Study group. One hundred forty-four consecutive patients (109 men; age: 40 to 94 years; mean age: 67 ± 9 years) who had undergone clinically indicated dobutamine stress echocardiography (DSE) were prospectively studied. The patients studied were consecutive and unselected. Clinical indications for DSE include the evaluation of the presence or severity of myocardial ischemia or myocardial viability. All patients had symptoms suggestive of angina. Seventy-eight patients had a previous history of myocardial infarction. Fifty-two patients had prior coronary revascularization. Medications were not withheld before DSE. Medication included nitrates in 89 patients, calcium channel antagonists in 45 patients, beta-blockers in 40 patients...
and angiotensin-converting enzyme inhibitors in 44 patients. Informed consent was obtained from all patients.

**DSE.** Dobutamine infusion started at 5 μg/kg per min and increased in 3-min stages up to 40 μg/kg per min. Atropine was given when required. End points for test termination were: 1) attainment of target heart rate; 2) completion of stress protocol; and 3) development of obvious echocardiographic abnormalities. Other reasons for terminating the test include: 1) arrhythmias such as ventricular tachycardia or sustained supraventricular tachyarrhythmias; 2) a substantial increase (>220 mm Hg) or decrease (<80 mm Hg) in systolic blood pressure; or 3) intolerable symptoms (12).

**TTDE.** Transthoracic Doppler echocardiography was performed using a commercially available ultrasound machine (SONOS 5500, Agilent Technologies, Andover, Massachusetts) with a broad-band high-frequency (5 to 12 MHz) transducer (S12). In B-mode color Doppler flow mapping, velocity was set in the range of ±12 to ±15 cm/s, and depth was adjusted at approximately 6 cm. Color Doppler detection of LAD flow was obtained as previously described (8,9). Briefly, the left ventricle was imaged in the low parasternal long-axis cross section, then the ultrasound beam was inclined laterally. Next, coronary blood flow in the distal portion of the LAD was identified as a color-filled tubular structure in the anterior interventricular sulcus under the guidance of Doppler color flow mapping. The long-axis sections were carefully adjusted to minimize the angle between the Doppler beam and the LAD flow. With a sample volume positioned on the color signal in the LAD in diastole, pulsed Doppler signal tracings of flow velocity in the LAD were recorded (Fig. 1).

**Echocardiography contrast enhancement.** The contrast agent for enhancing the left ventricular endocardial border delineation and Doppler flow signal in the LAD used in this study was Levovist (Tanabe Seiyaku, Inc., Tokyo, Japan and

![Image](image_url)

**Figure 1.** Color Doppler flow mapping of modified low parasternal long-axis view (top left) and spectral Doppler tracing (top right) in distal left anterior descending coronary artery (LAD) after contrast enhancement. Color-coded blood flow in the LAD is clearly seen (arrow). Spectral Doppler shows biphasic coronary flow with predominance of diastolic component. Middle and lower panels show an example of another patient with normal response. After infusion of dobutamine, coronary flow velocity gradually increased. Baseline diastolic mean velocity was 17.2 cm/s, and flow velocity increased to 54.4 cm/s after injection of atropine; thus, coronary flow velocity ratio peak is 3.16. Speed of recording 100 mm/s, velocity scale 80 cm/s. LV = left ventricle.
Schering AG, Berlin, Germany). The addition of 7 to 8 ml of sterile water into the 2.5 g of Levovist vial reconstituted 8 ml of Levovist solution (300 mg/ml). A 2-ml injection of Levovist was administered intravenously as a bolus followed by a slow saline flush from an in-dwelling cannula inserted into the antecubital vein.

**Study protocol.** At baseline, parasternal long- and short-axis views of the left ventricle in the second harmonic mode with a broad-band transducer (2 to 4 MHz, S4) was digitally acquired. Before the contrast injection, intermittent diastolic triggering every fifth or sixth cardiac beat in the apical four-chamber view was initiated. Focus was set at the level of the upper third of the left ventricle to prevent bubble destruction at the apex. Immediately after the left ventricular cavity was completely filled with contrast, we changed to the continuous harmonic imaging mode and digitally acquired an apical four- and two-chamber view. Next, the S12 probe was used to obtain distal LAD flow under the Doppler color flow mapping. The same procedure was repeated at 10 and 20 μg/kg per min of dobutamine infusion and peak stress. Stress two-dimensional images and CFV were also obtained at 5, 30 and 40 μg/kg per min of dobutamine infusion without contrast enhancement.

**Echocardiographic measurements.** Two-dimensional echocardiographic monitoring was performed throughout and up to 10 min after stopping the dobutamine infusion. Quad-screen format display was created by digitized four-standard imaging planes at baseline, during low dose of dobutamine infusion (10 μg/kg per min), intermediate dose (20 μg/kg per min) and at peak stress. These four images were also recorded on videotape at the end of each stage. Side-by-side comparison of wall motion in the digitized images was performed by one experienced investigator who was blinded to the patient's clinical data. Wall motion in each of the 16 segments of the left ventricle was scored, ranging from 0 = hyperkinesis, 1 = normal to 4 = dyskinesis. Segments were assigned to a vascular supply on the basis of a previously described model (13). A test result was considered positive for ischemia if stress induced an increase in the wall motion score in one or more segments, with the exception of a change from akinesis to dyskinesis (14). Wall motion abnormalities that remained fixed with stress were considered to represent infarction. The results of DSE were classified as positive for coronary artery disease if there was evidence of ischemia or infarction (12). For assessing regional wall motion in the LAD territory, nine segments (basal anteroseptal, basal anterior, midventricular septum, midanteroseptal, midanterior and four apical segments) were assigned to the LAD territory (13). These nine segmental scores were summed and divided by 9 to yield a regional wall motion score index (WMSI) at each stage. According to the results of wall motion response, the patients were divided into three subgroups: group I—patients who developed WMA up to intermediate dose (20 μg/kg per min) of dobutamine infusion; group II—patients who developed WMA at peak stress; and group III—patients whose baseline WMA improved or wall motion became hyperkinetic during dobutamine infusion.

Another experienced observer blinded to the clinical data performed CFV assessment. Measurements were made off-line by use of the built-in calculation package of the ultrasound unit. Diastolic flow envelope was traced, and mean diastolic velocity (MDV) was obtained at baseline and during each stage of dobutamine infusion. The CFV ratio (CFV ratio 5 [10, 20, 30, 40, peak]), defined as the ratio of MDV during 5 μg/kg per min of dobutamine infusion (10 μg/kg per min, 20 μg/kg per min, 30 μg/kg per min, 40 μg/kg per min and maximum dose), to basal MDV was calculated in each patient.

Interobserver measurement variability was determined by having a second independent observer measure Doppler velocity recordings at various stages in a group of 20 randomly selected patients. Intraobserver variability was determined by having one observer remeasure the spectral envelopes in 20 patients one month apart. Interobserver and intraobserver variabilities were calculated as the SD of the differences between two measurements and expressed as a percent of the average value (9).

**Statistical analysis.** Continuous data are expressed as mean ± SD. The differences among the three groups for the parametric data were tested by use of analysis of variance (ANOVA) and then for multiple comparisons using Fisher’s protected least-significance difference. Differences in WMSI and flow velocity between baseline and during dobutamine infusion were tested with ANOVA with repeated measures. Differences between two different parametric variables (heart rate, blood pressure) were tested with paired or unpaired t test, as appropriate. A simple linear regression analysis was performed between flow and wall motion variables. We examined the sensitivity and specificity of various cutoff points of the CFV ratio for predicting stress-induced WMA in the LAD territory. Using receiver operating characteristic curves, we defined the best cutoff value for its diagnosis. A probability level <0.05 was considered statistically significant.

**RESULTS**

**Doppler evaluation of CFV.** All patients completed DSE without serious complications. Under the guidance of color Doppler flow mapping, adequate spectral Doppler recordings of CFV in the distal portion of the LAD at baseline and during sequential infusion of dobutamine were obtained in 129 of 144 study patients (feasibility; 90%) (Fig. 1 and 2). Coronary flow velocity could be obtained up to the final stage of dobutamine infusion in 108 of 129 patients (84%) and one stage before the final stage in 18 patients (14%).

**Hemodynamics and wall motion.** In 129 patients with flow velocity recordings, maximum infusion rate of dobutamine was 20 μg/kg per min in 6 patients, 30 μg/kg per min in 28 patients, 40 μg/kg per min in 36 patients and 40 μg/kg per min with atropine in 59 patients, respectively.
Heart rate increased from 66 ± 12 beats/min at baseline to 127 ± 16 beats per min at peak stress (83% of age-predicted maximum heart rate); systolic blood pressure increased from 130 ± 20 mm Hg to 155 ± 33 mm Hg. Wall motion abnormality in the LAD territory was observed in 62 patients. Regional WMSI at baseline was 1.37 ± 0.52 at baseline, which decreased to 1.12 ± 0.68 at 10 μg/kg per min of dobutamine, 0.82 ± 0.77 at 20 μg/kg per min and 0.78 ± 0.84 at peak stress (p < 0.001, ANOVA). A total of 38 patients developed stress-induced WMA in the LAD territory. The number of patients in group I, group II and group III was 16, 22 and 91 patients. Wall motion score index at baseline was 1.77 ± 0.60 in group I, 1.47 ± 0.60 in group II and 1.28 ± 0.45 in group III, respectively (p < 0.001 group I vs. group III).

**Response of CFV.** Mean diastolic velocity was 15.4 ± 5.8 cm/s (range: 5.3 to 42.3 cm/s) at baseline and 34.9 ± 11.8 cm/s (range: 5.9 to 62.9 cm/s) at peak dose. The mean value of CFV ratio at peak stress (CFV ratio peak) was 2.39 ± 0.83 (range: 0.84 to 4.40), and CFV ratio peak was significantly lower in patients who developed stress-induced WMA in the LAD territory than it was in those without (1.51 ± 0.51 vs. 2.76 ± 0.65, p < 0.001). Coronary flow velocity ratio in the three subgroups of patients during sequential infusion of dobutamine is shown in Table 1. During dobutamine infusion, CFV ratio progressively increased in group III patients, in contrast with the blunted response in group I patients. Group II patients showed an intermediate response. The value of CFV ratio in group III at >20 μg/kg per min of dobutamine infusion became significantly higher than in group I and group II. Table 2 shows the relation between regional wall motion variables in the LAD territory and CFV ratio at each stage. At more than 10 μg/kg per min of dobutamine infusion, there was a significant correlation between WMSI at peak stress and CFV ratio (r = 0.30 to 0.62), and the best correlation was obtained using CFV ratio at peak stress. A significant correlation was also noted between ΔWMSI (WMSI at baseline minus WMSI at peak stress) and CFV ratio (r = 0.24 to 0.73). If analysis was confined to patients who had not taken beta-blockers or patients not administered atropine, these correlations were further improved, especially at low or intermediate dose of dobutamine. For predicting stress-induced WMA using CFV ratio, the best cutoff value of CFV ratio was defined at intermediate and peak dose of dobutamine infusion (Fig. 3). Coronary flow velocity ratio (at 20 μg/kg per min) <1.5 had a sensitivity of 68% (26/38) and a specificity of 81% (74/91) for the presence of stress-induced WMA in the LAD territory. Regarding the 17 false positive cases, 12 patients had taken beta-blockers. The sensitivity and specificity of CFV ratio peak <2.1 was 92% (35/38) and 86% (78/91), respectively. Regarding the three false negative cases of CFV ratio peak <2.1, two (CFV ratio peak = 2.97 and 2.57, respectively) had

### Table 1. CFV Ratio in the LAD During Dobutamine Infusion

<table>
<thead>
<tr>
<th>CFV ratio</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 μg/kg per min</td>
<td>1.04 ± 0.16</td>
<td>0.98 ± 0.14</td>
<td>1.05 ± 0.15</td>
<td>NS</td>
</tr>
<tr>
<td>10 μg/kg per min</td>
<td>1.33 ± 0.37</td>
<td>1.28 ± 0.25</td>
<td>1.39 ± 0.41</td>
<td>NS</td>
</tr>
<tr>
<td>20 μg/kg per min</td>
<td>1.32 ± 0.35*</td>
<td>1.51 ± 0.45*</td>
<td>2.08 ± 0.65</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>30 μg/kg per min</td>
<td>1.29 ± 0.38*</td>
<td>1.62 ± 0.51*</td>
<td>2.36 ± 0.68</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>40 μg/kg per min</td>
<td>1.00 ± 0.11†</td>
<td>1.65 ± 0.57*</td>
<td>2.52 ± 0.71</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>40 μg/kg per min + atropine</td>
<td>1.04 ± 0.12†</td>
<td>1.91 ± 0.19*</td>
<td>2.73 ± 0.62</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Peak dose</td>
<td>1.25 ± 0.34†</td>
<td>1.71 ± 0.53*</td>
<td>2.76 ± 0.65</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*p < 0.001 vs. group III; †p < 0.05 vs. group II.

ANOVA = analysis of variance; CFV = coronary flow velocity; LAD = left anterior descending coronary artery.
Table 2. Correlation Coefficient Between CFV Ratio and Wall Motion Score Variables

<table>
<thead>
<tr>
<th>CFV ratio</th>
<th>Vs. WMSI at Peak Stress</th>
<th>Vs. ΔWMSI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Beta (−)</td>
</tr>
<tr>
<td>5 μg/kg per min</td>
<td>r = 0.08</td>
<td>r = 0.06</td>
</tr>
<tr>
<td>10 μg/kg per min</td>
<td>r = 0.30*</td>
<td>r = 0.33†</td>
</tr>
<tr>
<td>20 μg/kg per min</td>
<td>r = 0.48* (129)</td>
<td>r = 0.54* (91)</td>
</tr>
<tr>
<td>30 μg/kg per min</td>
<td>r = 0.52* (111)</td>
<td>r = 0.56* (77)</td>
</tr>
<tr>
<td>40 μg/kg per min</td>
<td>r = 0.51* (84)</td>
<td>r = 0.55* (52)</td>
</tr>
<tr>
<td>Peak dose</td>
<td>r = 0.62* (129)</td>
<td>r = 0.62* (91)</td>
</tr>
</tbody>
</table>

*p < 0.001; †p < 0.01.
*Atropine (−) = not administered atropine; beta (−) = not taken beta-blocker; CFV = coronary flow velocity; ΔWMSI = WMSI at baseline − WMSI at peak stress; parenthesis = number of patients; WMSI = wall motion score index.

dobutamine-induced anterior wall ischemia, and the third had a CFV ratio peak of 2.12.

**Observer variability.** Interobserver and intraobserver variabilities for the measurements of CFV recordings were 5.6% and 6.5%, respectively.

**DISCUSSION**

This study showed that CFV in the distal LAD could be measured by TTDE in conjunction with a transpulmonary contrast agent in the majority of cases during dobutamine infusion. We also demonstrated that there was a close correlation between CFV response and wall motion changes. Coronary flow velocity ratio peak could accurately predict the presence of stress-induced WMA in the LAD territory (sensitivity, 92%; specificity, 86%). These results suggest that the application of CFV measurements during DSE provides additional noninvasive flow information on coronary circulation.

**Comparison with previous studies.** As far as we know, there are no published studies about CFV response during DSE.

**Figure 3.** Individual value bar graph representing coronary flow velocity (CFV) ratio at 20 μg/kg per min of dobutamine infusion (CFV ratio 20) and CFV ratio at peak stress (CFV ratio peak) for group I (development of stress-induced wall motion abnormality at intermediate dose), group II (wall motion abnormality at peak stress) and group III (normal response). Best cutoff line (dotted line) and mean value ± SD are also shown.
DSE by TTDE. Stoddard et al. (15) demonstrated the feasibility of pulsed Doppler dobutamine transesophageal echocardiography for measuring CFV in the proximal LAD and showed that Doppler coronary flow reserve and wall motion analysis were equally accurate for detecting significant LAD stenosis. However, most of the LAD stenoses are distal to the LAD segment visualized by transesophageal echocardiography. Flow velocity measured proximally to a stenosis may differ from poststenotic flow data, a phenomenon related to lower prelesional branch resistance that directs the flow away from or around the stenosis (2). Thus, CFVR assessed proximally to the stenosis may underestimate the functional significance of the stenosis severity.

**Current study.** We demonstrated that adequate quality of CFV in the distal LAD during DSE could be obtained in 90% of cases. The combined use of Levovist could improve not only left ventricular endocardial border delineation but also CFV envelope, thus allowing the simultaneous and noninvasive assessment of both wall motion and coronary flow in the LAD territory. Second, we also demonstrated that responses of CFV correlated well with the changes in wall motion during dobutamine infusion (Table 2). Our results reconfirmed the close relation between flow and function during dobutamine infusion (16,17). Third, this study showed that CFV ratio was already lower in patients who developed stress-induced WMA than it was in those without, even at an intermediate dose of dobutamine infusion (20 μg/kg per min of dobutamine). That is, there is a relationship between intermediate-dose abnormalities in CFV ratio and the eventual ischemic response, and it may be that abnormalities of CFV ratio are detected earlier than ischemic wall motion responses. However, there is much overlap of CFV ratio at an intermediate dose of dobutamine between patients with and without stress-induced WMA compared with CFV ratio at peak stress. This overlap is partly because 30% of patients in this study had taken a beta-blocker. Beta-blockers are known to attenuate flow velocity response of dobutamine, especially at low and intermediate doses. Another possibility is that the development of flow abnormality and WMA is a continuum. Hence, lag time may be short between the onset of detectable flow abnormality and subsequent ischemic wall motion response. Nevertheless, early detection of abnormal coronary flow response may facilitate accurate diagnosis of stress-induced WMA. Fourth, the value of CFV ratio at peak stress in patients with normal response of DSE was nearly the same as previously reported CFVR values obtained in patients without significant LAD stenosis during adenosine infusion (6,9–11) but lower than that in normal volunteers (7). Although the mechanisms by which dobutamine and adenosine augment coronary flow are distinctly different, our results suggest that intravenous dobutamine at doses used for stress testing could also induce maximal vasodilation in patients with coronary artery disease (18,19). Further comparative study is needed to validate these findings.

**Study limitations.** Some potential methodological limitations need to be addressed in this study. First, we calculated CFV ratio based on diastolic CFV, not on CFV during the entire cardiac cycle, but previous studies also calculated CFVR by diastolic CFV (5,6,8–11). It is difficult to obtain a complete diastolic flow envelope in some patients, especially when heart rate >130 beats/min. Augmentation of myocardial contractility and increase in heart rate produces a wall motion ghost on the color flow mapping, which makes it difficult to position the sample volume in the LAD. Maintenance of the same tomographic plane, Doppler angle and depth of the sample volume throughout the examination is mandatory to overcome these problems.

Second, the use of a contrast agent greatly improved the feasibility of CFV recording, but it produces a bubble noise. As they disintegrate into the blood stream, agents such as Levovist appear to aggregate into larger collections of gas, which are capable of producing a “spike” in the Doppler spectrum when bubbles are destroyed by the ultrasound energy. The bubble noise affects accurate tracing of flow envelope in some cases. Reducing the transmission power can eliminate some of this noise.

Third, this method was only applicable in the distal part of the LAD. If patients have isolated diagonal branch stenosis, there could be a discrepancy between CFV ratio and induced WMA. Whether this method is applicable in the other coronary arteries remains to be determined.

Fourth, although we tried to minimize the angle between the Doppler beam and the LAD flow, we did not perform angle correction in the Doppler measurement. Hence, there may have been underestimation of the true velocity. However, for the purpose of CFV ratio, the absolute velocity value was not needed because CFV ratio is a quotient of two velocities.

**Clinical implications.** This new diagnostic approach, the combined use of TTDE and contrast-enhanced DSE has potential in several clinical conditions. It may enhance the reliability of wall motion analysis, especially when the development of WMA is subtle. Because of its noninvasive nature, it has a potential for the serial assessment of flow and function in patients before and after coronary revascularization. It can be used for detecting LAD stenosis in those conditions such as left bundle branch block, in which assessment of wall motion alone is difficult or not reliable. This approach also has merit for assessing myocardial viability in patients with chronic left ventricular dysfunction during low-dose dobutamine infusion.

**Conclusions.** Assessment of CFV in the distal LAD during DSE was feasible in the majority of cases, and velocity-derived values correlated well with dobutamine-induced wall motion changes. Coronary flow velocity ratio can identify patients who have developed wall motion abnormalities. These results suggest that CFV measurements in the distal LAD could provide another source of information for detecting stress-induced myocardial ischemia. Further studies are needed to validate its potential.
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REFERENCES