New Noninvasive Method for Coronary Flow Reserve Assessment
Contrast-Enhanced Transthoracic Second Harmonic Echo Doppler

Carlo Caiati, MD; Cristiana Montaldo, MD; Norma Zedda, MD; Alessandro Bina, MD; Sabino Iliceto, MD

Background—We tested the hypothesis that blood flow velocity could be recorded in the left anterior descending coronary artery (LAD) during transthoracic echocardiography by use of second harmonic echo Doppler modality along with contrast enhancement (intravenous Levovist) at rest and after pharmacologically induced maximal vasodilation to assess coronary flow reserve (CFR) with a totally noninvasive approach.

Methods and Results—Fifty-six consecutive patients undergoing coronary angiography underwent transthoracic contrast-enhanced pulsed-wave Doppler recording of blood flow velocity in the LAD by use of harmonic color Doppler as a guide at rest and after maximal vasodilation by dipyridamole infusion. Contrast enhancement with the harmonic mode greatly improved the success rate of recording adequate pulsed-wave Doppler signal in the LAD. CFR was (mean±SD) 1.54±0.7 in patients with (group 1) and 2.79±0.9 in patients without (group 2) significant LAD stenosis (lumen narrowing >70%) (P<0.001); sensitivity and specificity in detecting significant LAD stenosis were 86% and 90%, respectively. There was close agreement between CFRs determined by this new method and intracoronary Doppler flow wire.

Conclusions—Contrast-enhanced transthoracic echo Doppler with the harmonic mode is a feasible and promising technique for assessing CFR in a totally noninvasive way. (Circulation. 1999;99:771-778.)

Key Words: blood flow ▪ coronary disease ▪ contrast media ▪ echocardiography

Coronary flow reserve (CFR) assessment is a clinically useful method to assess coronary function. Several methods have been established for measuring CFR.1 However, these methods are invasive (intracoronary Doppler flow wire),2 semiinvasive (transesophageal Doppler echocardiography3), or extremely expensive and thus scarcely available (PET).4

The left anterior descending coronary artery (LAD) can be visualized by means of transthoracic cross-sectional echocardiography. Transthoracic blood-flow Doppler recording has been attempted in the distal part by use of high-frequency transducers.5 However, the success rate in evaluating distal LAD blood flow is so low6 that this method has never been proposed for CFR assessment.

Intravenously injected echo-contrast agents improve Doppler signal-to-noise ratio in the coronaries by enhancing signal amplitude.6,7 Second harmonic technology, a recently introduced imaging ultrasound modality, further improves the enhancing effect of echo-contrast agents by reducing noise without reducing the signal from the blood.8 Thus, we undertook this study to verify the following hypotheses: (1) coronary blood flow velocity in the LAD can be measured during a transthoracic Doppler study in baseline conditions and after pharmacologically induced maximal vasodilation with an echo-contrast agent capable of enhancing Doppler signal intensity, signal-to-noise ratio, and a nonlinear response when pulsating in an ultrasound field with second harmonic Doppler technology; (2) CFR assessed by this approach is useful in detecting significant LAD stenosis; and (3) CFR assessment is in agreement with CFR assessed by a gold-standard method, such as intracoronary Doppler flow wire.2

Methods

Study Group
Fifty-six consecutive patients (42 men; age, 32 to 84 years; mean age, 59±11 years) scheduled for diagnostic coronary angiography were prospectively studied. The patients studied were consecutive and unselected; thus, those with large body habitus were also included. All patients underwent coronary angiography because of suspected or known coronary artery disease. Twenty-one had experienced previous myocardial infarction. All coronary active medications were withdrawn the morning of the echocardiographic study. Of the 56 patients, 23 had significant (>70% narrowing) stenosis affecting the proximal (13 patients [2 occlusions]), middle (7 patients...
or distal (3 patients) portion of the LAD (group 1); the remaining 33 patients (group 2) did not have significant LAD stenosis. All patients were informed of the purpose and nature of the study and provided informed consent.

**Study Protocol**

Each patient underwent a color-guided pulsed-wave (PW) Doppler recording of coronary blood velocity in the LAD in baseline condition and after dipyridamole administration (0.54 mg/kg IV over 4 minutes, followed by 4 minutes of no dose and then 0.28 mg/kg over 2 minutes) both before and after contrast enhancement. Two separate infusions of the echo-contrast agent were given: 1 for the baseline and 1 for the dipyridamole part of the study. The second contrast infusion was started a few seconds after the dipyridamole administration protocol was finished. Coronary flow evaluation was performed with fundamental color Doppler before contrast infusion and with second harmonic color Doppler during contrast infusion.

**Transthoracic Echocardiography and Color Doppler**

Echocardiography was performed with a prototype release of the Acuson Sequoia ultrasound unit (Acuson Corp) by use of a broadband transducer with second harmonic capability (3V2c). B-mode and contrast-enhanced color Doppler imaging was performed in the second harmonic mode (1.7 MHz transmitting and 3.5 MHz receiving), whereas color-coded Doppler before contrast enhancement and spectral Doppler were performed in fundamental imaging at 2.5 MHz.

All studies were continuously recorded on a 0.5-in super-VHS videotape, and significant portions were also captured in a cineloop format or still frames and digitally stored to simplify off-line reviewing and measurements.

A systematic attempt was made to record flow in the distal or middle part of the LAD. The approach for the distal part consisted first of obtaining a short axis of the left ventricular apex and anterior groove to search for coronary flow. When a diastolic circular color-coded blood flow was recognized in the anterior groove area, the transducer was rotated clockwise to obtain the best long axis of color flow. Alternatively, a modified foreshortened 2-chamber view was obtained by sliding the transducer superiorly and medially from an apical 2-chamber position (Figure 1). Then, a careful search for color-coded blood flow was made over the epicardial part of the anterior wall with simultaneous attempts to optimize the visualization of the anterior groove area by very slight counterclockwise

![Figure 1. Color Doppler flow mapping in distal LAD before (A, top) and after (A, bottom) contrast enhancement. Modified 2-chamber view was obtained. B, Artist’s drawing of this tomographic plane orientation to LAD. Before contrast infusion, no LAD flow is detected by color Doppler in fundamental mode in anterior groove area. After contrast infusion, second harmonic color-coded blood flow in LAD is clearly depicted (arrows). LV indicates left ventricle; SVC, superior vena cava; AO, aorta; RA, right atrium; and RV, right ventricle.](http://circ.ahajournals.org/)

[1 occlusion], or distal (3 patients) portion of the LAD (group 1); the remaining 33 patients (group 2) did not have significant LAD stenosis. All patients were informed of the purpose and nature of the study and provided informed consent.
rotation and medial angling of the probe. The middle part of the LAD was visualized by a low parasternal short-axis view of the base of the heart modified by a slight clockwise rotation of the transducer beam. If no color-coded blood flow from the LAD was visualized in the baseline condition, the same procedure was attempted again during contrast enhancement.

Spectral Doppler
PW Doppler recording was attempted with color flow as a guide, with sample volume positioning in diastole. Spectral trace of coronary flow velocity was characterized by a biphasic flow with a prevalent diastolic component (Figure 2). If a relatively high (>50 cm/s) baseline velocity was recorded, probably indicating acceleration at the stenosis site, a second Doppler recording (reference value) was performed in a different arterial segment. The first baseline velocity was discarded if it was 50% higher than the reference value. This occurred in 2 group 1 patients.

Echo-Contrast Enhancement
The Doppler signal enhancer used in this study was Levovist (Schering AG). The echo-contrast agent was administered by infusion with a devoted infusion pump (IVAC P4000 anesthesia syringe pump) connected over a special 50-cm connector tubing to an in-dwelling cannula (20 to 22 gauge) inserted into a cubital vein. On the basis of our previous experiences, we used a concentration of 300 mg/mL. Regarding infusion rate, we started with 1 mL/min of a volume of 6 to 7 mL; this rate was increased to a maximum of 2 mL/min or decreased to a minimum of 0.5 mL/min according to the quality and entity of the Doppler signal enhancement achieved. Contrast administration was performed both before and after intravenous dipyridamole administration.

Echocardiographic Measurements
Feasibility of blood-flow-velocity Doppler recording in the LAD (both harmonic color and spectral Doppler) was evaluated in all protocol steps by the consensus of 2 experienced observers using a 3-grade scoring system previously validated in our laboratory. Briefly, the following scoring system was used. For color Doppler, 1 = no color Doppler signal detected in the LAD, 2 = suboptimal color Doppler signal (width <1 mm), and 3 = optimal color-coded Doppler signal (width >1 mm). For spectral Doppler, 1 = no signal detection, 2 = spectral signal recognizable but with poor definition of the outline of the diastolic and systolic waves, and 3 = optimal outline definition of at least the diastolic curve. The duration of contrast enhancement (visually assessed) was timed by use of a built-in chronometer of the ultrasound unit activated at the start of contrast infusion. CFR assessment was performed by 1 experienced operator blinded to the clinical and angiographic data. Measurements were made off-line by use of the built-in calculation package of the ultrasound unit. The following coronary flow velocity parameters were measured before and after dipyridamole: peak and mean diastolic velocity and peak and mean systolic velocity. For each parameter, the highest 3 (in case of sinus rhythm; n =52) or 6 (in case of atrial fibrillation; n =2) cycles were averaged. CFR was calculated as the ratio of hyperemic to basal peak (peak CFR) and mean (mean CFR) diastolic flow velocity.

Left ventricular mass was calculated by use of the modified formula of Devereux et al.

Interobserver measurement variability was determined by having a second independent observer measure Doppler velocity recordings in 10 patients. Intraobserver variability was assessed by having 1 observer remeasure spectral curves 1 month apart in 10 patients as well. Intraoperator and interoperator reproducibility of velocity data acquisition was assessed by repeating measurements in 13 and 9 LAD segments, respectively. For this purpose, evaluations were performed by the same operator and by 2 different operators, respectively, 2 times, 2 hours apart.

Reproducibility of the angle between LAD flow direction and the ultrasound spectral Doppler beam in baseline conditions and during dipyridamole vasodilation was assessed in the first 33 patients enrolled in the study for both the rest and dipyridamole parts of the study.

Figure 2. Spectral Doppler tracing by sampling in distal LAD before (top left) and after (top middle) contrast enhancement at rest and after dipyridamole infusion (top right). Before contrast infusion, spectral Doppler signal is not detectable (score =1). After contrast enhancement, biphasic flow with prevalent diastolic component is clearly depicted both at rest and after dipyridamole (score =3). Bottom, In same patient, intracoronary Doppler flow wire tracings at rest (bottom left) and after adenosine (bottom right) are presented. Coronary flow velocity is almost identical, and CFR is the same (4.3) by 2 methods. Curve shapes at baseline are also similar.
Coronary Angiography
All coronary angiograms were blindly read, and calipers were used in cases of questionable findings. Any LAD angiographic obstruction >70% was considered a significant stenosis.

Doppler Flow Wire
In a subgroup of 16 patients (17 cases overall because 1 patient was studied before and after coronary angioplasty), intravascular velocity measurement in the LAD, distal to the eventual stenosis, was attained by means of a 0.014-in. 14-MHz Doppler guide wire (Flower Wire Cardiometrics, Inc) at rest and after hyperemic stimulus as previously described. Care was taken to avoid placement in a side branch or poststenotic velocity jet. Spectral Doppler signal was then recorded at baseline and after an 18-μg IC bolus of adenosine. Hyperemic stimulus was repeated at least twice. In most cases, premedication with either intracoronary (200 μg) or sublingual (0.4 mg) nitroglycerin was performed. CFR was computed as the ratio of hyperemic to basal average peak velocity.

All intravascular Doppler studies except 1 (postangioplasty case) were performed within 48 hours of transthoracic Doppler examinations by a researcher blinded to the transthoracic Doppler results.

Statistical Analysis
Continuous data are expressed as mean±SD. Differences in Doppler score before and after contrast enhancement were tested by use of a χ2 analysis (contingency table, 3 rows times 2 columns). The differences between the 2 groups for the parametric and categorical data were tested by use of an unpaired 2-tailed t test and a χ2 test, respectively. Differences between baseline and hyperemic data were tested overall by use of an unpaired 2-tailed t test and within groups by use of a paired 2-tailed t test. Sensitivity and specificity for CFR as a predictor of significant LAD stenosis were calculated in the traditional manner.

Intraobserver interobserver measurement variability and reproducibility and comparison of CFR evaluated by the 2 methods were evaluated by use of both a linear regression analysis expressed as the correlation of coefficients (r) and SEE and the Bland-Altman method for assessing the limits of agreement between the repeated measurements.

Results
No significant difference was found between the 2 study groups in terms of demographic and clinical characteristics and left ventricular mass.

Blood flow velocity in baseline conditions and after dipyridamole vasodilation was attempted first in the distal LAD. If no (3 patients) or an unsatisfactory (9 patients) recording was obtained in the distal segment, recording was attempted in the middle portion (12 patients). In 1 patient (from group 1), blood flow velocity recording during dipyridamole vasodilation was not achieved, so this patient was excluded from CFR evaluation (CFR feasibility, 98%).

Effect of Contrast Enhancement on Color and Spectral Doppler
The use of contrast agent greatly improved both second harmonic color (Figure 1) and PW Doppler recording feasibility (Figure 2) in the LAD (Table 1).

The contrast-enhancing effect peaked at ≈3 minutes after the infusion was begun and remained constant until the end of the infusion. The duration of the enhancement at rest and after dipyridamole was 8±5 and 6±5 minutes, respectively, depending on the total injected volume and infusion rate.

### Table 1. Color and PW Doppler Quality Before and After Contrast Enhancement

<table>
<thead>
<tr>
<th></th>
<th>Score=1</th>
<th>Score=2</th>
<th>Score=3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Color flow, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before enhancement*</td>
<td>24 (43)</td>
<td>24 (43)</td>
<td>8 (14)</td>
</tr>
<tr>
<td>After enhancement</td>
<td>0 (0)</td>
<td>2 (4)</td>
<td>54 (96)</td>
</tr>
<tr>
<td><strong>Dipyridamole</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before enhancement*</td>
<td>31 (56)</td>
<td>20 (34)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>After enhancement</td>
<td>1 (2)</td>
<td>3 (5)</td>
<td>52 (93)</td>
</tr>
<tr>
<td><strong>PW Doppler, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before enhancement*</td>
<td>18 (32)</td>
<td>34 (61)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>After enhancement</td>
<td>0 (0)</td>
<td>2 (4)</td>
<td>54 (96)</td>
</tr>
</tbody>
</table>

*P<0.001, score before vs score after contrast enhancement.

Dipyridamole Infusion
No major adverse reactions occurred after dipyridamole infusion. Slight modifications of heart rate and systolic blood pressure were observed after dipyridamole infusion. Heart rate and systolic blood pressure increased 17±10 bpm (from 65±13 to 81±14 bpm [P<0.01]) and 5±15 mm Hg (from 128±19 to 133±23 mm Hg [P<0.05]). Diastolic blood pressure did not change at all. This response was similar in the 2 groups.

Transthoracic CFR Versus Angiography
Blood flow velocity was similar in the 2 groups in the baseline conditions (Table 2). After dipyridamole infusion,
blood flow velocity increased much more in group 2 (Figure 2) than in group 1 (Figures 3 and 4 and Table 2). Consequently, peak and mean diastolic CFRs were much higher in group 2 than in group 1 (Figure 4). A CFR for peak diastolic volume <2.0 had a sensitivity of 86% and a specificity of 90% for the presence of significant LAD stenosis. Notably, the 2 patients from group 2 with the lowest hyperemic-to-normal-flow-velocity ratio (1.57 and 1.53) had 60% stenosis of the mid-LAD, a positive exercise 201 Tl scan for moderate apical and anterior ischemia, and a normal LAD with typical effort angina. This last patient underwent intracoronary Doppler flow wire in the LAD (Table 3, patient 5) that confirmed the abnormal CFR value in the absence of coronary stenosis. Of the 3 false-negative patients in group 1 (Figure 4), 2 had distal LAD stenoses and the other had a LAD proximal occlusion.

Of the 3 patients with LAD occlusion, 1 had a middle occlusion, and CFR was evaluated in the midportion of the vessel (proximal to the stenosis) because no flow was detected in the distal part; the other 2 showed proximal occlusion immediately after a stenotic and a normal, respectively, diagonal branch leading to the apex. The CFRs for these 2 patients, very likely obtained in the diagonals, were blunted and normal, respectively.

**Transthoracic Versus Intracoronary CFR**

CFR as assessed with this new method closely agreed with intracoronary Doppler flow wire CFR ($r=0.88$). In all but 2 cases, the difference between intracoronary and transthoracic CFR was a maximum of 0.3 (Figure 5). Overall, the upper and lower limits of agreement between the 2 approaches were 0.83 (95% CI, 0.43 to 1.25) and −0.8 (95% CI, −1.21 to −0.39), respectively.

**Intraobserver and Interobserver Variability and Reproducibility and Angle Variability**

Intraobserver and interobserver variabilities in tracing curve outlines were low (Table 4). Intraobserver and interobserver reproducibility of blood flow velocity recording was high (Table 4). There was no significant variation of $\theta$ angle between baseline (11.6±12 grades) and dipyridamole (11.4±13 grades [P=NS]) recordings.

**Discussion**

This study demonstrates that transthoracic harmonic color Doppler and PW Doppler, in conjunction with intravenous injection of an echo-contrast agent with appropriate ultrasound characteristics, allows detection of LAD blood flow and, more importantly, its accurate measurement in baseline conditions and during dipyridamole vasodilation, thus providing a totally noninvasive assessment of CFR. PW Doppler recording of optimal quality (score 3) was achieved in 96% of patients at baseline and in 89% during dipyridamole infusion after contrast enhancement and in only 7% and 4%, respectively, before contrast enhancement ($p<0.001$). CFR assessed with this new method can accurately predict the presence of a significant (>70% narrowing) LAD stenosis (sensitivity, 86%; specificity, 90%) and is in strict agreement with CFR as assessed by intracoronary Doppler flow wire.
It is highly reliable and reproducible method for assessing CFR² (Figures 2 and 5 and Table 3).

Echo Doppler Assessment of Coronary Flow and Reserve

A semiinvasive approach to CFR with ultrasound was first proposed by Iliceto et al¹ some years ago. However, this approach required transesophageal intubation of an ultrasound probe to be obtained.⁷ In the last few years, scattered reports⁵ have indicated that the distal LAD can be visualized by a transthoracic approach by use of a high-frequency transducer. However, the success rate of visualizing the artery and the flow, especially in unselected populations, was extremely low (between 18% and 56%). Interestingly, our precontrast feasibility data (Table 1) parallel those of these reports.

Echo-Doppler Enhancement:
Methodological Considerations

The high success rate in detecting coronary flow in the LAD relies on the combination of contrast enhancement and

TABLE 3. Angiographic Findings and CFR Values by Both IDFW and Enhanced TTE in 17 Patients

<table>
<thead>
<tr>
<th>Patient Initials</th>
<th>Age, y</th>
<th>Sex</th>
<th>Stenosis Severity, %</th>
<th>LAD Location</th>
<th>CFR IDFW</th>
<th>Enhanced TTE</th>
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<tr>
<td>1 P.G.</td>
<td>45</td>
<td>M</td>
<td>&lt;20*</td>
<td>Middle</td>
<td>2.7</td>
<td>2.6</td>
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<tr>
<td>2 S.U.</td>
<td>63</td>
<td>M</td>
<td>60</td>
<td>Proximal</td>
<td>2.3</td>
<td>2.4</td>
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<tr>
<td>3 F.A.</td>
<td>59</td>
<td>M</td>
<td>70</td>
<td>Middle</td>
<td>2.1</td>
<td>1.9</td>
</tr>
<tr>
<td>4 P.M.†</td>
<td>72</td>
<td>F</td>
<td>&lt;20*</td>
<td></td>
<td>2.4</td>
<td>2.3</td>
</tr>
<tr>
<td>5 P.M.†</td>
<td>70</td>
<td>F</td>
<td>0</td>
<td></td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>6 C.P.</td>
<td>55</td>
<td>M</td>
<td>&lt;20</td>
<td>Proximal</td>
<td>2.8</td>
<td>2.7</td>
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<td>7 M.M.</td>
<td>54</td>
<td>M</td>
<td>40</td>
<td>Middle</td>
<td>4.3</td>
<td>4.3</td>
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<tr>
<td>8 B.G.</td>
<td>68</td>
<td>M</td>
<td>65</td>
<td>Middle</td>
<td>2.2</td>
<td>3.4</td>
</tr>
<tr>
<td>9 G.G.</td>
<td>66</td>
<td>M</td>
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<td>3.1</td>
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<tr>
<td>10 S.B.</td>
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<td>M</td>
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<tr>
<td>11 P.L.</td>
<td>70</td>
<td>M</td>
<td>75</td>
<td>Middle</td>
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<td>1.6</td>
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<tr>
<td>12 L.A.†</td>
<td>53</td>
<td>M</td>
<td>85</td>
<td>Middle</td>
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<td>1.3</td>
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<tr>
<td>13 L.A.</td>
<td>53</td>
<td>M</td>
<td>&lt;20*</td>
<td>Middle</td>
<td>3.2</td>
<td>3.3</td>
</tr>
<tr>
<td>14 S.A.‡</td>
<td>58</td>
<td>M</td>
<td>&lt;20</td>
<td>Middle</td>
<td>1.5</td>
<td>1.6</td>
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<tr>
<td>15 L.E.</td>
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<td>M</td>
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<td></td>
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<tr>
<td>16 C.M.</td>
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<td>M</td>
<td>50</td>
<td>Middle</td>
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<tr>
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<td>F</td>
<td>0</td>
<td></td>
<td>3.1</td>
<td>3.2</td>
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</table>

IDW indicates intracoronary Doppler flow wire; TTE, transthoracic Doppler.

*Postangioplasty evaluation.
†Patient with mitral regurgitation and effort angina.
‡Complicated PTCA.

Figure 5. Left, Relation between CFR obtained with 2 methods: transthoracic Doppler (TTE, x axis) and intracoronary (y axis) Doppler flow wire (DFW). Lines of equality (dotted line) and correlation (continuous line) are drawn. Right, Difference between CFRs obtained by 2 methods against their mean. Dotted lines represent boundaries of mean±2 SD.
second harmonic technology. Contrast enhancement has been proved useful in increasing Doppler signal-to-noise ratio in coronaries by increasing signal amplitude.6,7 In addition, harmonic Doppler imaging with echo-contrast agents capable of nonlinear emission of harmonics can further increase the signal-to-noise ratio by eliminating flashing and clutter artifacts coming from the tissue without significantly reducing the signal from blood.8 In the harmonic mode, the echoes in second harmonic frequency coming from the resonant contrast agent are received, whereas echoes from the solid tissue and red blood cells in fundamental frequency (containing noise) are suppressed or attenuated. Thus, a contrast-dependent image is produced.

Color Doppler recording of coronary blood flow is of crucial importance because it allows more appropriate PW sample volume positioning. We administered contrast by infusion and not by bolus because infusion has the advantage of maintaining the enhancing effect of the agent over several minutes.

CFR and Stenosis Severity
The good separation of the 2 patient groups (with and without significant LAD stenosis) with CFR as assessed with this new method (Figure 4) was related mainly to the homogeneously reduced hyperemic blood flow response in the group with significant LAD stenosis (except for the 3 false-negative). This was likely determined by measurement of CFR in the poststenotic segment. Coronary flow velocity and CFR measured distal rather than proximal to a coronary stenosis is a more precise index of flow response not being influenced by nonnarrowed branching arteries11 whose presence can pseudonormalize flow response to a vasodilating agent.

Study Limitations
CFR assessment can be invalidated if measurements are performed at the stenosis site. In our study, however, to circumvent this problem, a second Doppler sampling (reference value) was obtained in a different portion of the artery in patients with relatively high baseline velocity (>50 cm/s), possibly indicating acceleration at the stenosis site.

In a certain number of cases, the θ angle was quite large (>30°), causing underestimation of the true velocity. However, for the purpose of the CFR evaluation, the absolute velocity value was not needed because CFR is a quotient of 2 velocities. In our study, there was no significant difference between the θ angle at baseline and during dipyridamole recording.

We measured a CFR index using a simple ratio of 2 velocities. This, as previously pointed out by others,12 is a reliable indicator of CFR.

In patients with coronary occlusion and distal LAD stenosis, false-negative studies may arise. Erroneous sampling in a LAD branch (occlusion) or in a prestenotic segment (distal stenosis) is a likely explanation.

In some of our patients without significant LAD stenosis, CFR individual values show a certain scatter, with an average value that appears to be lower than the normal CFR values already reported in other animal and human studies that used a variety of techniques.13 This can be explained by taking in account the fact that our “control group” included patients scheduled for coronary angiography because of chest pain. In these patients, CFR can theoretically be impaired because of several causes, such as X syndrome, that can increase resistance to coronary blood flow (see patient 5 in Table 3).

Methodological limitations could explain some discrepancies with intravascular Doppler flow wire. In particular, in the 2 patients with the largest CFR discrepancy, sampling proximal to the LAD stenosis by transthoracic Doppler (Table 3, patient 8) and a lower vasodilator effect of dipyridamole with respect to adenosine14 (Table 3, patient 9) could very likely explain the difference in CFR measurements.

Clinical Implications
This totally noninvasive method to assess CFR has potentially interesting clinical applications. It may provide additional information to cardiac catheterization in the assessment of LAD coronary stenoses, especially those of intermediate anatomic severity whose functional impact can be precisely assessed only with the poststenotic CFR evaluation.11 It may also be useful in the noninvasive detection of LAD stenosis in situations, such as a left bundle-branch block, in which stress tests (both scintigraphy and echocardiography) are not reliable because of the high number of the false-positive studies; in assessing microcirculation impairment in conditions affecting CFR in the absence of coronary artery disease; and because of the possible serial evaluation, for exploring short- and long-term effects of various therapeutic interventions, such as coronary angioplasty, on CFR.

In conclusion, the combined use of echo-contrast agents and second harmonic technology can succeed in detecting coronary blood flow and measuring flow and reserve in humans in a totally noninvasive way. Because of its noninvasive nature, this new method has potential in both pathophysiologic and clinical studies. Larger studies are needed.
to investigate its potential in various diseases with possible CFR impairment.

Acknowledgments
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