Contrast-Enhanced Transthoracic Second Harmonic Echo Doppler With Adenosine

A Noninvasive, Rapid and Effective Method for Coronary Flow Reserve Assessment

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OBJECTIVES
The purpose of this study is to evaluate the feasibility in detecting blood flow in the left anterior descending coronary artery (LAD) using transthoracic color Doppler (CD) imaging (in both second harmonic and fundamental mode) along with contrast enhancement and to verify if this new noninvasive method along with adenosine is safe, rapid and effective in assessing coronary flow reserve (CFR).

BACKGROUND
Feasibility of contrast-enhanced transthoracic Doppler recording (in both second harmonic and fundamental mode) of blood flow velocity in the LAD has not been assessed. Adenosine has a greater vasodilator potency and more favorable kinetics than dipyridamole and thus it can be more suitable for assessing CFR in conjunction with this method.

METHODS
Sixty-one patients with angiographically patent LAD underwent CD (both in fundamental and harmonic mode) as well as color-guided pulsed wave (PW) Doppler recording of blood flow velocity in the distal LAD before and after intravenous contrast injection. A second group of patients (n = 77), undergoing coronary angiography, was submitted to transthoracic contrast-enhanced PW Doppler recording of blood flow velocity in the LAD using harmonic CD as a guide, at rest and during adenosine-induced hyperemia.

RESULTS
Harmonic CD along with echo contrast consistently improved blood flow detection in the LAD; the success rate in detecting flow of optimal quality was 88% with this approach, whereas it was 11% and 16% with CD in fundamental mode, respectively, before and after contrast. Pulsed wave Doppler results paralleled those of harmonic CD (p < 0.001 contrast harmonic vs. fundamental). In the second group of patients coronary angiography revealed 0% to <40% stenosis in 24 patients (group I), ≥40% to ≤75% in 17 patients (group II) and >75% stenosis in 34 patients (group III). There was a significant difference in CFR among the three groups of patients; CFR for peak diastolic velocity was (mean ± SD): 2.88 ± 0.7 (group I), 2.09 ± 0.5 (group II) and 1.51 ± 0.5 cm/s (group II) (p < 0.05 group I vs. both group II and group III; p < 0.05 group II vs. group III). The whole examination took less than 10 min.

CONCLUSIONS
Contrast-enhanced second harmonic Doppler recording of blood velocity in the LAD is highly feasible and in combination with adenosine it is a rapid, safe and effective method for assessing CFR ratio. (J Am Coll Cardiol 1999;34:122–30) © 1999 by the American College of Cardiology

Coronary flow reserve (CFR) evaluation is important for understanding pathophysiology of coronary circulation. However, actual available and established methods for assessing CFR are either invasive (intracoronary Doppler flow wire) (1), highly expensive and scarcely available (positron emission tomography) (2) or semi-invasive and scarcely feasible (transesophageal Doppler) (3,4), thus their clinical use is largely hampered.

Recently, we have demonstrated that blood flow and reserve can be evaluated in the distal left anterior descending coronary artery (LAD) using a noninvasive (transthoracic) enhanced Doppler examination (5). The enhancement of Doppler signal is attained using an ultrasound contrast agent capable of nonlinear response along with a new ultrasound Doppler technology, second harmonic Doppler imaging, that further increases Doppler signal to noise ratio from coronaries by reducing noise and clutter from tissue. In this previous study (5), however, an intraindividual comparison of the feasibility in obtaining coronary blood flow velocity by fundamental versus harmonic contrast-enhanced
color Doppler was not systematically attempted; furthermore, dipyridamole was used as hyperemic stimulus. Dipyridamole has intrinsic limitations for CFR assessment, especially if it is used in a contrast echocardiographic study such as ours. Since it takes a long time (several minutes) to reach the maximal effect, contrast infusion has to be discontinued after getting the baseline curves and a second infusion of contrast has to be started after dipyridamole administration. This implies that dipyridamole coronary flow recording cannot be monitored continuously throughout the study as a period of no enhancement occurred. This shortcoming can make it difficult to keep the plane orientation constant in order to have the same theta angle throughout the study. Thus, this approach is technically challenging and, in addition, quite a large amount of contrast has to be used for each study. On the other hand, since it takes time for the dipyridamole-induced side effects to reverse, an antidote must be injected at the end of study in most patients.

Intravenous adenosine is superior in inducing maximal coronary vasodilation (6) and thanks to its rapid action may overcome most of the shortcomings inherent in using dipyridamole (relatively long duration of the study, need for two separate infusions of contrast, reimagining coronary flow during hyperemia, need for an antidote). It is not known whether intravenous adenosine in conjunction with enhanced transthoracic Doppler can be useful in assessing CFR and in predicting LAD stenosis severity as assessed by coronary angiography.

Thus we undertook a study to: 1) evaluate, in a large series of patients, the feasibility of the method in recording blood flow velocity in the LAD comparing intraindividually color Doppler in fundamental versus color Doppler in harmonic mode; and 2) verify if this new Doppler method is a superior means to assess CFR and predict LAD coronary stenosis as assessed by coronary angiography.

METHODS

Study group. To evaluate the feasibility of the method, 64 consecutive patients scheduled for diagnostic coronary angiography were prospectively studied. Patient accrual took place from July to December 1997. The patients studied were consecutive and unselected, and thus also included those with large body habitus. Angiography was performed in all patients and only those with patent LAD (n = 61) were included in the final analysis. [The underlying cardiovascular diseases were coronary artery disease in 41 patients of which 20 with previous myocardial infarction, suspected X syndrome in 6 patients, severe aortic valvulopathy in 2 patients, cardiomyopathy in 3 patients and systemic hypertension in 9 patients.] Coronary active medication regimen was not modified before the echocardiographic Doppler study.

To evaluate the potential of the method with adenosine in assessing CFR, a second study group of 77 consecutive patients (61 men; aged 32 to 79 years; mean age 59 ± 9) undergoing diagnostic coronary angiography for chest pain was accrued from March to August 1998. Patients with dilated cardiomyopathy, significant valvular diseases and severe left ventricular hypertrophy were excluded. Due to the results of coronary angiography, the patients were divided into three subgroups. Group I consisted of 36 patients with 0% to <40% coronary stenosis. Group II consisted of 18 patients with ≥40 to ≤75% LAD diameter stenosis and group III consisted of 23 patients with diameter lumen narrowing >75%.

All patients were informed of the purpose and nature of the study and they provided informed consent.

Transthoracic echocardiography and color Doppler. Echocardiography was performed with a prototype release of the Acuson Sequoia ultrasound unit (C256 Echocardiography System, Acuson Corporation) using a broadband transducer with second harmonic capability (3V2c). Contrast-enhanced color Doppler imaging was performed both in fundamental (2.5 MHz) and 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. Color-coded Doppler setting was adjusted for maximizing scanning sensitivity (pulse repetition frequency was reduced) without importantly reducing the frame rate. All studies were continuously recorded on a half-inch (1.27 cm) S-VHS videotape.

Color Doppler detection of LAD flow was obtained in the distal or in the midpoint of the LAD as previously described (5). Briefly, the approach for the distal part consisted first in obtaining a short-axis view of the left ventricular apex and of the anterior groove to search for coronary flow (7) (Fig. 1A, C and D). When diastolic circularly shaped color-coded blood flow was recognized in the anterior groove area, the transducer was rotated clockwise to obtain the best long-axis view of color flow (Fig. 1B and E). Alternatively, a modified foreshortened two-chamber view was obtained by sliding the transducer superiorly and medially from an apical two-chamber position (Fig. 1F and G). Then, a careful search for color-coded blood flow was attempted over the epicardial part of the anterior wall trying at the same time to optimize the visualization of the anterior groove area by very slightly rotating counterclockwise and medially angling the probe. The midpoint 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 (Fig. 1H and I).
Figure 1. Artist’s drawing illustrating transducer beam orientations to the left anterior descending coronary artery (LAD) (A, B, F, H) with the corresponding echocardiographic images of LAD color flow (C–E, G, I): in particular panels A and B indicate tomographic plane orientation for attaining, respectively, a parasternal short- and long-axis view of the distal LAD. Color flow visualized with this approach is represented in panels C, D (short-axis views of color flow) and E (long-axis view of color flow); panel F indicates the transducer orientation for a more apical approach still for the distal LAD (color flow visualized with this approach is represented in panel G); panel H is the tomographic orientation for the visualization of the midtract of the LAD (color flow visualized with this approach is represented in panel I). AO = aorta; CF = color flow; LA = left atrium; LV = left ventricle; MV = mitral valve; RA = right atrium; RV = right ventricle; RVOT = right ventricular outflow tract; SVC = superior vena cava.
If no color-coded blood flow from LAD was visualized in the baseline condition, the above-described procedure was again attempted during contrast enhancement.

**Spectral Doppler.** To measure coronary flow velocity, color-coded flow imaging was first attained, and then pulsed wave (PW) Doppler recording was attempted using color flow as a guide. The gate size was set at 4.0 mm. If the angle between color flow and Doppler beam was higher than 20°, angle correction was performed using the software package included in the ultrasound unit. Sample volume positioning was performed taking into account the diastolic position of the vessel (4). Spectral trace of coronary flow velocity was characterized by a biphasic flow with a prevalent diastolic component (Fig. 2).

**Echocontrast enhancement.** The Doppler signal enhancer used in this study was Levovist (Schering AG, Berlin, Germany) (8). The echo contrast agent was administered by infusion using a devoted infusion pump (IVAC P4000 Anaesthesia Syringe pump) connected over a special 50-cm connector tubing (Medrad, Indianola, Pennsylvania) to an indwelling cannula (20 to 22 g) which was inserted into a cubital vein.

On the basis of our previous experiences, we used a concentration of 300 mg/ml (5). Regarding infusion rate, we started with 1 mg/min of a volume of 6 to 7 ml; during the same infusion 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.

**Fundamental versus harmonic mode: Study protocol.** Each patient underwent color Doppler and color-guided PW Doppler evaluation of blood flow velocity in the LAD before and after contrast administration. Before contrast color Doppler was performed in fundamental mode only, whereas after contrast it was performed both in fundamental and in second harmonic mode. After contrast administration, PW sample volume positioning was guided using the best color flow either in fundamental or in second harmonic mode.

**Coronary flow reserve study protocol.** In the second study group of 77 patients, blood flow Doppler recording in the LAD was first attempted at the baseline (fundamental mode) and after contrast enhancement (harmonic mode); then, during the same contrast infusion, intravenous adenosine (140 μg/kg per min over 5 min) was started using a separate intravenous line. Recording of hyperemic flow velocity by PW Doppler was started as soon as color signal showed increment of velocity (brighter color hue or appearance of aliasing) or in any case, within 2 min from the beginning of the drug administration and continued until the fifth minute. If during adenosine the theta angle or LAD segment appeared different than that visualized at baseline, a new baseline velocity curve was recorded 5 min after stopping adenosine infusion, making sure to maintain constant monitoring of the adenosine view throughout the washout phase.

**Echocardiographic measurements.** Feasibility of blood flow velocity Doppler recording in LAD before and after Levovist infusion was assessed both qualitatively using a scoring system (this was used for both color and spectral Doppler) and quantitatively by measuring the length of the detected color Doppler signal (in both fundamental and harmonic mode).

Color and PW Doppler signals were scored by the consensus of two expert observers by using a previously validated three-grade scoring system partially modified in this study (9). Briefly, regarding color Doppler, the following scoring system was used. Score 1: LAD color Doppler signal was either not detected or not evaluated because of an intense blooming effect that blurred LAD color flow signal. Score 2: suboptimal color Doppler signal owing to either a scarcely depicted signal (width <1 mm) or to a blooming artifact that made LAD color flow detection difficult. Score 3: optimal delineated color-coded Doppler signal (width
The following scoring system was used for spectral Doppler. Score 1: no signal detection. Score 2: spectral signal recognizable, but with poor definition of the outline of the diastolic and systolic waves. Score 3: optimal outline definition of at least the diastolic curve. Color Doppler flow signal length (in both fundamental and harmonic mode) was assessed by measuring the maximal recorded length of color Doppler flow signal using calipers (9).

CORONARY FLOW RESERVE MEASUREMENT. One experienced echocardiographer blinded to the angiographic results performed blood flow velocity measurement. Measurements were made off-line, using the built-in calculation package of the Acuson Sequoia ultrasound unit.

The following coronary flow velocity parameters were measured before and during hyperemia in the subgroup of patients undergoing CFR assessment: peak and mean diastolic velocity peak. For each parameter the highest of three (in case of sinus rhythm: 75 cases) or six cycles (in case of atrial fibrillation: two cases) was averaged. Coronary flow reserve was calculated as the ratio of hyperemic to basal peak (peak CFR) and mean (mean CFR) diastolic flow velocity.

Coronary angiography. An experienced independent observer who was unaware of the patients’ clinical status or echocardiographic Doppler results visually read all coronary angiograms. Calipers were used when questionable findings arose. Coronary artery disease was defined as a diameter lumen narrowing >75%.

Intraobserver–interobserver variability and reproducibility. Intra- and interobserver variability and reproducibility in obtaining and measuring coronary flow velocity by transthoracic Doppler have been previously assessed and reported (5).

Statistical analysis. Continuous data are expressed as mean ± 1 SD. The differences among three different dependent samples (LAD length in three different conditions) or three different independent samples (namely, peak and mean diastolic velocity and CFR in the three groups) were tested at first with analysis of variance (ANOVA) for repeated measures and one-way ANOVA (or Kruskall-Wallis ANOVA on ranks in case Normality test failed), respectively, and then for multiple comparisons with Student-Newman-Keuls test or Dunn’s method in case of parametric or nonparametric ANOVA, respectively. Differences between two different parametric variables (heart rate, blood pressure) were tested with paired or unpaired t test as appropriate. Differences in Doppler score before and after contrast enhancement (categorical variables) were tested using a chi-square analysis (contingency table, three rows × two columns). Sensitivity and specificity for CFR as a predictor of significant LAD stenosis were calculated in the traditional manner.

A probability value \( p < 0.05 \) (or \( p < 0.01 \) when multiple comparisons of categorical data were attempted) was considered significant.

RESULTS

Doppler evaluation of coronary flow. In the first group of 62 patients blood flow velocity was recorded in the distal LAD in 52 and in the midportion of the remaining nine patients, because distal blood flow was not attainable at all in three patients or it was of poor quality in six patients even after contrast enhancement. In the precontrast examinations, feasibility in recording blood flow in the LAD by Doppler was poor (Fig. 3, Table 1). Echo contrast considerably increased CD signal intensity in the LAD, improving blood flow Doppler recording in this vessel. However,
significantly better results with color Doppler were achieved when contrast was used along with second harmonic mode (Fig. 3, Table 1). In three patients, the enhancing effect of contrast was higher when fundamental color Doppler was used rather than color Doppler in harmonic mode. In one of these patients the midportion of the LAD was visualized. Color Doppler length was considerably increased after contrast injection, especially when color Doppler in harmonic mode was used. After echo contrast injection color flow length increased from (mean ± SD) 5.7 ± 6 mm to 14.6 ± 11 mm (fundamental), and 19 ± 7 mm (harmonic) (p < 0.01 contrast-enhanced studies vs. baseline). Having a longer length of the vessel displayed along with a clearer depicted signal was of aid in best positioning sample volume for spectral Doppler recording. Thus, color-guided PW Doppler recording consistently improved after contrast injection with results that closely paralleled those obtained with contrast-enhanced harmonic color Doppler (Fig. 3, Table 1). Systolic flow was recorded, in the contrast studies, in 67% of patients. During the precontrast study (even if color flow was not detectable), a suboptimal (score 2) spectral trace was obtained in four patients by blindly performing PW Doppler sampling. This can be attributed to the low temporal resolution of color Doppler. Conversely, PW Doppler in the distal LAD for one patient was still undetectable after contrast enhancement for a disturbing “wall thumps” artifact on the spectral trace despite a good harmonic color Doppler delineation of the vessel blood flow.

Contrast infusion modalities. In most patients, a contrast infusion rate of 1 ml/min offered the best results in terms of enhancement. In only a few patients a higher or lower infusion rate was attempted. Using an infusion rate of 1 ml/min, a clinically useful signal enhancement was achieved ≈3 min after starting the infusion. The enhancing effect remained constant or in some cases improved just a little during the rest of the infusion.

<p>| Table 1. Color and Pulsed Wave Doppler Quality Before and After Contrast Enhancement |
|-----------------------------------------------|------------|------------|------------|</p>
<table>
<thead>
<tr>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color flow Before C</td>
<td>24 (39%)</td>
<td>30 (49%)</td>
</tr>
<tr>
<td>After C Fundamental</td>
<td>14 (23%)</td>
<td>37 (61%)</td>
</tr>
<tr>
<td>Second harmonic*</td>
<td>0 (0%)</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>PW Doppler Before C†</td>
<td>22 (36%)</td>
<td>34 (56%)</td>
</tr>
<tr>
<td>After C</td>
<td>1 (2%)</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>

*p < 0.001 vs. both color flow score before contrast and color flow score in fundamental mode after contrast enhancement. †p < 0.001 vs. pulsed wave Doppler score after contrast enhancement. Data presented are number (%) of patients.

C = contrast enhancement; PW = pulsed wave Doppler.
Coronary flow reserve assessment in predicting LAD stenosis severity. In the second group of patients (n = 77) in whom CFR was assessed, blood flow velocity in baseline conditions and during adenosine infusion was attempted first in the distal LAD. If no or unsatisfactory recording was obtained in the distal segment, recording was attempted in the midportion (four patients).

Contrast enhancement along with harmonic mode greatly enhanced the success rate in recording adequate PW Doppler signal from the LAD. This signal was, in fact, assessable in only 55% of patients before contrast and in all patients after contrast enhancement (p < 0.01), giving a CFR feasibility of 100%. Baseline velocities were similar in the three subgroups of patients (Table 2). However, during hyperemia, velocity increased differently, giving a significantly different mean CFR value among the three groups (Table 2, Fig. 2). Regarding the individual CFR values in the three groups, good separation was attained between group I and III, whereas group II largely overlapped with the three groups, giving a CFR value among the three groups.

Regarding the two false negative cases in group III (Fig. 4), one had both a normal high dose dobutamine echo and pharmacologic single photon emission computed tomographic myocardial perfusion imaging and the other had the stenosis located in the distal LAD segment.

Adenosine infusion. No major adverse reactions occurred after adenosine. Twenty patients reported hypereanpnea that tended to abate by the end of the infusion.

Slight modification of heart rate was observed after adenosine. Heart rate increased from 65 ± 10 to 81 ± 13 bpm (p < 0.05). Arterial pressure did not show a significant change after adenosine (126 ± 20 mm Hg systolic and 79 ± 11 mm Hg diastolic at rest and 126 ± 21 mm Hg systolic and 78 ± 12 mm Hg diastolic during

### Table 2. Blood Flow Velocity and CFR Determined in the Left Anterior Descending Coronary Artery

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control state</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDV (cm/s)</td>
<td>32 ± 11</td>
<td>39 ± 16</td>
<td>30 ± 11</td>
</tr>
<tr>
<td>MDV (cm/s)</td>
<td>25 ± 8</td>
<td>29 ± 10</td>
<td>23 ± 10</td>
</tr>
<tr>
<td><strong>Adenosine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDV (cm/s)</td>
<td>87 ± 21*</td>
<td>79 ± 27*</td>
<td>47 ± 26</td>
</tr>
<tr>
<td>MDV (cm/s)</td>
<td>68 ± 16*</td>
<td>59 ± 20*</td>
<td>38 ± 20</td>
</tr>
<tr>
<td>CFR for PDV</td>
<td>2.88 ± 0.7*</td>
<td>2.09 ± 0.5*</td>
<td>1.51 ± 0.5</td>
</tr>
<tr>
<td>CFR for MDV</td>
<td>2.87 ± 0.7*</td>
<td>2.13 ± 0.7</td>
<td>1.64 ± 0.7</td>
</tr>
</tbody>
</table>

*p < 0.05 vs. group III. †p < 0.05 vs. groups II and III.

CFR = coronary flow reserve; MDV = mean diastolic velocity; PDV = peak diastolic velocity.

### DISCUSSION

This study demonstrates, first, that in a large nonselected series of patients, harmonic and not fundamental Doppler aids in improving blood flow velocity transthoracic Doppler recording in the LAD, during contrast enhancement and second, that adenosine in combination with this new method allows rapid assessment of CFR reserve with a high success rate (100%) and good prediction of significant coronary stenosis (specificity and overall sensitivity 91% and 76%, respectively) as assessed by coronary angiography.

Evaluation of coronary flow by contrast-enhanced fundamental and second harmonic Doppler: Methodologic considerations. In contrast Doppler studies performed in fundamental mode, the wash-in of the contrast agent in the explored cavity often produces such disturbing phenomena as blooming and flashing which partially or completely obscure the image details (Fig. 3, middle panel). Therefore, blood flow from coronary vessels even if detected can be swamped by these artifactual color signals (10). In our study, clutter artifacts and blooming of color image after contrast appearance impeded clear color signal detection in fundamental mode in most of the patients (in 61% the color Doppler signal was suboptimal [score 2] and in 23% still completely undetectable [score 1]). On the other hand, second harmonic ultrasound technology eliminates the artifacts without affecting the signal from blood because it exploits the nonlinear motion of microbubbles when exposed to an ultrasound field. Using second harmonic Doppler technology, a contrast-dependent image is produced; in fact, the echoes in second harmonic frequency coming from

### Figure 4. Individual value bar graph indicating CFR for group I (LAD stenosis 0% to <40%), group II (LAD stenosis ≥40 to ≤75%) and group III (LAD stenosis >75%). Mean (± 1 SD) values are also shown. Abbreviations as in Figure 3.

adenosine [p = NS]]. This response was similar in the three groups.
the resonant contrast agent are received, whereas echoes from the solid tissue as well as from the red blood cells in fundamental frequency (containing noise) are suppressed or attenuated.

Whether our results can be duplicated with different contrast agents and harmonic imaging systems remains to be proved.

**Adenosine and coronary flow reserve assessment.** Technical aspects. Intravenous adenosine seems superior to dipyridamole for use in conjunction with this new contrast-enhanced Doppler method for inducing hyperemia and thus assessing CFR. First, in fact, thanks to adenosine rapid action (peak effect in 55 ± 33 s vs. 287 ± 101 with dipyridamole) (6), the hyperemic part of the study is short (2 to 3 min) and consequently only one contrast infusion (11 ml volume) is required to cover both the baseline and the hyperemic part of the examination. Second, because the enhancement of Doppler signal is uninterruptedly obtained throughout the study, Doppler recording is more easily and accurately performed. Third, unlike dipyridamole, adenosine in doses >100 μg/kg has been shown to be nearly equivalent to papaverine to produce maximal coronary vasodilation. Fourth, the short duration of the examination in association with the prompt reversibility of the side effects, if any, after termination of the infusion with no need for an antidote make this drug safe and very well accepted by the patient and thus eventually repeatable during the same study.

The only shortcoming of adenosine was the frequently induced hyperpnea (in 20 of our patients). This side effect, however, was never disturbing for the patient and rarely caused degradation of image quality, thus severely impairing Doppler coronary flow velocity recording.

**Prediction of coronary stenosis.** Coronary flow reserve assessed with this new method is successful in predicting coronary stenosis severity in the LAD and almost no overlapping occurred between the groups with obstructive (group III) and 0% to <40% stenosis (group I) (Fig. 4). The good prediction of coronary stenosis in group III mainly relies on having very likely assessed CFR in the poststenotic segments (in 95% of the patients distal LAD was in fact evaluated). Post-stenotic CFR accurately reflects the residual vasodilating capacity of that vascular bed which is specifically affected by the stenosis (11). In contrast, prestenotic CFR can be diagnostically unreliable because the abnormal response in the post-stenotic territory can be pseudonormalized by the normal vasodilating response in the territories supplied by the branching vessels stemming off the main trunk between the sampling zone and the stenosis. The two outliers in group III can be explained by sampling prestenotically in a patient with distal LAD stenosis and by a probable overestimation of the real vessel narrowing with angiography, since the patient had negative stress tests (both high dose dobutamine echo and adenosine single photon emission computed tomography).

However, in the group of patients with intermediate coronary stenosis (group II), even if the mean CFR value was significantly lower and higher than that in the groups with obstructive or no stenosis, respectively, the single values largely overlapped with the other two groups. This result is not unexpected given the poor correlation of angiography with coronary function especially in the subset of intermediate coronary stenoses (12). On the other hand, that CFR evaluated by our method is reliable is supported by the fact that it is strictly in agreement with CFR evaluated by the intracoronary Doppler flow wire ($r = 0.89$) (5).

The specificity for significant coronary stenosis was lower (76%) than that attained in our previous study (90%), where a separate analysis for the intermediate stenosis group, however, was not performed (5). A different percentage of patients with intermediate coronary stenosis in the two studies (12% vs. 23%) can mainly account for the discrepancy.

**Study limitations.** The method presented in this report for the noninvasive evaluation of blood flow velocity and reserve within LAD presents some limitations. First, CFR assessment can be invalidated if measurements are performed at the stenosis site (8). Second, blood flow can be visualized mainly in the LAD. Whether this Doppler method can be applied for assessing CFR in other coronary arteries remains to be explored. Third, flow in the LAD branches could be erroneously interpreted as the flow in the main trunk. In particular, this could happen in the two-chamber or in the short-axis view, where, respectively, a long diagonal branch or the first septal perforator (13) might also be visualized. Fourth, B-mode vessel visualization was not clearly assessable with our probe spatial resolution (3.5 MHz), so absolute blood flow calculations were not performed. However, the lack of this parameter is not central for CFR assessment in that during hyperemia, vessel size does not change with respect to the baseline so vessel size cancels out.

**Clinical implications.** This new method, being noninvasive, rapid and reliable in assessing coronary flow reserve, has potential in several clinical conditions, especially for serial assessment of CFR. It can be used for detecting LAD stenosis in those conditions such as left bundle branch block, in which traditional stress testing (with or without imaging) is not reliable.

It also has potential in the evaluation and follow-up of blood flow dynamics and flow reserve in several conditions such as X syndrome, aortic regurgitation (14), cardiomyopathies (15,16), left ventricular hypertrophy and hypertension and pericardial constriction (17), in which blood flow dynamics and/or CFR can be impaired in the absence of atherosclerotic narrowing of major epicardial vessels.

Lastly, it can be used in all conditions (such as myocardial infarction with LAD reopening and LAD percutaneous transluminal coronary angiography) in which follow-up of
different interventions aimed at ameliorating coronary flow in general and microcirculation function in particular is of crucial importance.

CONCLUSIONS

This study has demonstrated in a large series of patients that contrast-enhanced transthoracic Doppler echocardiography in harmonic mode rather than in fundamental mode allows detection and measurement of blood flow in the LAD at rest and after pharmacologic interventions and that intravenous adenosine along with enhanced Doppler is a superior means of measuring CFR ratio. Thanks to its complete noninvasiveness and consequently easy, bedside repeatability, this method has great potential for a repeated, serial evaluation of flow velocity and flow reserve in humans.

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