Validation of a New Noninvasive Method (Contrast-Enhanced Transthoracic Second Harmonic Echo Doppler) for the Evaluation of Coronary Flow Reserve

Comparison With Intracoronary Doppler Flow Wire

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OBJECTIVES
We tested the hypothesis that coronary flow reserve (CFR) in the left anterior descending coronary artery (LAD) as assessed by a new noninvasive method (contrast-enhanced transthoracic second harmonic echo Doppler) is in agreement with CFR measurements assessed by intracoronary Doppler flow wire.

BACKGROUND
Contrast-enhanced transthoracic second harmonic echo Doppler is a novel noninvasive method to detect blood flow velocity and reserve in the LAD. However, it has not yet been validated versus a gold-standard method.

METHODS
Twenty-five patients undergoing CFR assessment in the LAD by Doppler flow wire were also evaluated by contrast-enhanced transthoracic Doppler to record blood flow in the distal LAD at rest and during hyperemia obtained by adenosine IV infusion. In five patients CFR was evaluated twice (before and after angioplasty).

RESULTS
As a result of the combined use of IV contrast and second harmonic Doppler technology, feasibility in assessing coronary flow reserve equaled 100%. The agreement between the two methods was high. In fact, in all but five patients the maximum difference between the two CFR measurements was 0.38. Overall, the prediction (95%) interval of individual differences was $-0.69$ to $+0.72$. Reproducibility of CFR measurements was also high. The limits of the agreement (95%) between the two measurements were $-0.32$ to $+0.32$.

CONCLUSIONS
Coronary flow reserve in the LAD as assessed by contrast-enhanced transthoracic echo Doppler along with harmonic mode concurs very closely with Doppler flow wire CFR measurements. This new noninvasive method allows feasible, reliable and reproducible assessment of CFR in the LAD. (J Am Coll Cardiol 1999;34:1193–200) © 1999 by the American College of Cardiology

Coronary flow reserve (CFR) is an important functional parameter to understand the pathophysiology of coronary circulation. However, a large-scale assessment of this important functional parameter is hampered by the lack of a reliable, low-cost, noninvasive method. In fact, the available methodologies in assessing CFR are either invasive (intracoronary Doppler flow wire [IDFW]) (1) or expensive and scarcely available (positron emission tomography) (2). Some years ago transesophageal echocardiography (TEE) was proposed for assessing CFR in humans (3). However, this method bears some important limitations: it is seminvasive, it has suboptimal feasibility in visualizing flow in the left anterior descending coronary artery (LAD) (ranging from 69% to 89%) and it can allow only the assessment of prestenotic CFR in coronary artery disease (CAD) patients.

Distal LAD, having a superficial course close to the anterior chest wall, can be visualized by transthoracic echocardiography (TTE). Several studies have in fact demonstrated the potential of TTE for this purpose. Unfortunately, in these studies the feasibility in visualizing flow in distal LAD was low, hampering clinical applicability of the method for CFR.

Doppler signal from coronaries can be enhanced by using intravenously injected contrast agents that survive transpul-
Abbreviations and Acronyms

CAD = coronary artery disease
CFR = coronary flow reserve
IDFW = intracoronary Doppler flow wire
LAD = left anterior descending coronary artery
PTCA = percutaneous transluminal coronary angioplasty
PW = pulsed wave
TEE = transesophageal echocardiography
TTE = transthoracic echocardiography

Monetary passage. Harmonic Doppler can further enhance Doppler signal-to-noise ratio by reducing the noise coming from the tissue without reducing Doppler signal intensity (4,5). We have recently demonstrated that blood flow velocity Doppler recording during a transthoracic study can be greatly improved using contrast and second harmonic Doppler technology; CFR as assessed by this new method can very well predict significant stenosis affecting the LAD, and in a small, preliminary series of patients, using dipyridamole as vasodilator, it agrees with an independent reference method such as IDFW (6).

However, this new promising method has yet to be validated versus a gold-standard method such as IDFW in a larger series of patients using adenosine as hyperemic stimulus, a more effective and safer agent than dipyridamole, nor is its reproducibility in obtaining such flow reserve measurements known. Thus, we undertook this study to establish 1) the agreement between this noninvasive method (baseline-adenosine contrast-enhanced transthoracic Doppler) with IDFW in assessing CFR in the LAD, and 2) the reproducibility of CFR measurements as assessed by this new method.

METHODS

Study group. Twenty-five patients (21 men; ages 44 to 79; mean age 60 ± 8 years) undergoing cardiac catheterization and intravascular Doppler flow wire in the LAD were prospectively studied. The patients were submitted to IDFW for diagnostic purposes. The enrollment was carried out in a consecutive way on the basis of the catheterization laboratory decision of performing the IDFW study. This implied that even patients with large body habitus were included. All patients underwent coronary angiography because of suspected or known CAD. Ten patients had experienced a previous myocardial infarction. All coronary active medications were withdrawn the morning of the laboratory decision of performing the IDFW study. This implied that even patients with large body habitus were included. All patients underwent coronary angiography because of suspected or known CAD. Ten patients had experienced a previous myocardial infarction. All coronary active medications were withdrawn the morning of the echocardiographic study. All transthoracic Doppler studies were performed within 24 h from the intracoronary Doppler study. Seventeen of the 25 patients had a stenosis affecting either the proximal, mid- or the distal portion of the LAD. Eight out of 17 patients with LAD stenosis underwent coronary angioplasty, and IDFW was performed before and after angioplasty in five and only after angioplasty in three patients. 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, Mountain View, California) using a broadband transducer with second harmonic capability (3V2c). Its broad bandwidth allows transmission and reception of ultrasound frequencies over a wide range (from 2 to 3.5 MHz) of values both for B-mode and Doppler modality. During contrast administration only color Doppler was performed in second harmonic mode, whereas pulsed-wave (PW) Doppler was still obtained in fundamental. The B-mode was obtained in second harmonic mode (1.7 MHz transmitting frequency and 3.4 MHz receiving) throughout the study to improve image quality.

A systematic attempt was performed to record flow in the distal LAD (Fig. 1) in order to have maximal changes to measure flow velocity distally to a possible stenosis (24 patients). If blood flow was not clearly detectable in the distal portion, the midpart of the LAD was approached (1 patient). Color Doppler detection of LAD flow was obtained as recently described (6).

Spectral Doppler. To measure coronary flow velocity, color-coded flow imaging was attained, and then PW Doppler recording was attempted using color flow as a guide. If the angle between color flow and Doppler beam was higher than 20° (two patients), angle correction was performed using the software package included in the ultrasound unit. Sample volume positioning was performed taking the diastolic position of the vessel into account (3). Spectral trace of coronary flow velocity was characterized by a biphasic flow with a prevalent diastolic component (Fig. 2). If a relatively high (>50 cm/s) baseline velocity was recorded, likely 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 (7).

Echo contrast enhancement. The Doppler signal enhancer used in this study was Levovist (Schering AG, Berlin, Germany) (7), a suspension of monosaccharide (galactose) microparticles in sterile water. The echo contrast agent was administered by infusion using a devoted infusion pump (IVAC P4000 Anaesthesia Syringe pump, Hampshire, United Kingdom) connected over a special 50-cm connector tubing (Medrad, Medrad, Indiana, Pennsylvania) to an indwelling cannula (20 to 22 gauge), which was inserted into a cubital vein.

Intensity of enhancement is related to two contrast parameters: concentration and infusion rate. On the basis of previous experience, we used a concentration of 300 mg/ml (7,8). Regarding infusion rate, we started with 1 mg/min of a volume of 6 to 7 ml. This rate, during the same infusion, 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 at baseline and during drug induced hyperemia.

**Transthoracic CFR study protocol.** Each patient underwent a color-guided PW Doppler recording of coronary blood velocity in the LAD in baseline condition and after pharmacologic hyperemic stimulus: in 23 studies IV adenosine (0.14 mg/kg per minute for 5 min) was used as a hyperemic agent, whereas in the other 7 studies, IV dipyridamole (0.54 mg/kg over 4 min followed by 4 min of no dose and then 0.28 mg/kg over 2 min). When adenosine was used, ultrasound contrast was administered simultaneously. Thus, two separate IV lines were used. The baseline part of the adenosine study was obtained in the first minute of Doppler enhancement before commencing simultaneous adenosine infusion.

In contrast, when dipyridamole was used, two separate infusions of the echo contrast agent were given: one for the baseline and the other for the dipyridamole part of the study. No simultaneous administrations of contrast and dipyridamole were performed. The second contrast infusion was started a few seconds after terminating dipyridamole administration protocol. Coronary flow evaluation was performed using fundamental color Doppler before contrast infusion and using second harmonic color Doppler during contrast infusion.

**Echocardiographic measurements.** The CFR assessment was performed by one experienced echocardiographer.
blinded to the clinical and angiographic data. 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: peak and mean diastolic velocity peak and mean systolic velocity. For each parameter the highest 3 (in case of sinus rhythm: 29 cases) or 6 cycles (in case of atrial fibrillation: 1 case) were averaged. The CFR was calculated as the ratio of hyperemic to basal peak (peak CFR) and mean (mean CFR) diastolic flow velocity.

Reproducibility of CFR measurements was assessed by repeating CFR evaluation twice, 1 h apart, by the same operator in a subgroup of 13 patients. The reproducibility study was carried out only with adenosine, and the second CFR was assessed only if the first evaluation had not induced ischemia or side effects in the patient.

Coronary angiography. An experienced independent observer who was unaware of patients’ clinical status or echocardiographic Doppler results visually read all coronary angiograms. Stenosis severity was expressed, as usual, in terms of percent diameter narrowing. Calipers were used in case of questionable findings.

Doppler flow wire. Intravascular velocity measurement in the LAD was attained by means of a 0.014-in., 14-MHz Doppler guide wire (FloWire, Cardiometrics, Inc.) at rest and after hyperemic stimulus. In all patients but one, intracoronary Doppler velocity measurement was performed after transthoracic harmonic Doppler study. The intracoronary Doppler guide wire was advanced through the guiding catheter to a position 2 to 3 cm distal to the stenotic lesion if present. Otherwise, it was placed in a proximal LAD site. Care was taken to avoid placement in a side branch or post-stenotic velocity jet. Spectral Doppler signal was then recorded at baseline and after 18-μg intracoronary bolus of adenosine (9). Hyperemic stimulus was repeated at least twice. Curves without optimal delineation of both systolic and diastolic waves were discarded. Doppler flow velocity spectra were automatically analyzed online to determine time-averaged peak velocity. Coronary flow reserve was then computed as the ratio of hyperemic to basal average peak velocity. If repeated CFR measurements in the same patients gave discordant results, an average CFR value was considered.

Statistical analysis. Continuous data are expressed as mean and standard deviation (SD). Two-way repeated-measures ANOVA (analysis of variance) (Statistica, Version 5, 1997, Statsoft, Inc.) with two repeated-measures factors (i.e., drug intervention [no drug vs. drug] and type of Doppler examination [transthoracic vs. intracoronary Doppler]) was used to test for the effects and interactions of the different levels of these two factors on the hemodynamic variables (namely heart rate and systolic and diastolic blood pressure). The Newman–Keuls test was used for post hoc analysis.

Correlation between CFRs measured by the two methods and by the same method was evaluated using both a linear regression analysis expressed as the correlation of coefficient (r) and the Bland–Altman method for assessing the limits of agreement between the repeated measurements (10).

RESULTS

Doppler curves suitable for the analysis were obtained in all patients (CFR feasibility: 100%). In five patients CFR measurements were performed twice (before and after percutaneous transluminal coronary angioplasty [PTCA]) by both methods. Overall, 30 CFR measurements were compared.

Hemodynamic data. No major adverse reactions occurred during hyperemia. Heart rate was higher during the transthoracic Doppler compared with the intracoronary Doppler study owing to the adenosine effect (F for interaction = 52; p < 0.01) (Table 1). Systolic blood pressure was not different between the two Doppler methods, nor did adenosine have a significant effect (Table 1). Diastolic blood pressure was constantly and significantly lower during the transthoracic Doppler compared with the intracoronary Doppler (52; p < 0.01) and adenosine did not cause any significant change to this variable (Table 1).

Transthoracic versus intravascular CFR. Coronary flow reserve as assessed by this new method closely agreed with IDFW CFR (Figs. 3 and 4). In all but five patients, in fact, the difference between intracoronary and transthoracic CFR was a maximum of 0.38 (Fig. 5; Table 2). Overall, the prediction interval (95%) of individual differences was 0.72 (95% confidence interval [CI], 0.43 to 1.03) and −0.69 (95% CI, −0.99 to −0.39). Considering CFR as a categorical variable (normal or abnormal on the basis of a largely
accepted cutoff value of 2) (11), the agreement between the two methods was 97%. In the patient with the largest CFR measurement disagreement (Patient 1 in Table 2), coronary angiography revealed a “very distal” mid-LAD stenosis and a long diagonal branch stemming off the LAD proximally to the stenosis and leading to the apex.

**DISCUSSION**

This study demonstrates that transthoracic harmonic color Doppler and PW Doppler in conjunction with IV injection of an echo contrast agent with appropriate ultrasound characteristics (4) offers feasible, reliable and reproducible evaluation of blood flow velocity in the LAD at rest and during hyperemia, allowing accurate CFR determination in the LAD in a completely noninvasive way.

The CFR measurements are strictly in agreement with CFR as assessed by IDFW (limits of agreement: $-0.69$ to $+0.72$), a highly reliable and reproducible method in assessing CFR (9,12) (Fig. 5). The reproducibility of measurements of CFR was high ($r = 0.97$) (Fig. 6).

**Echo-Doppler enhancement: Methodologic considerations.** The high success rate in detecting coronary flow in the LAD relies on the combination of contrast enhancement with second harmonic technology. Contrast enhancement has proved to be useful in increasing Doppler signal-to-noise ratio in coronaries by increasing the amplitude of the signal (7,8). 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 (4,5).

Color Doppler recording of coronary blood flow is of crucial methodologic importance in measuring flow in that it allows optimal color-coded flow detection in the LAD and, thereby, more appropriate PW sample positioning (Figs. 1 and 2). We administered contrast by infusion and not by bolus. This administration modality of the echo contrast agent has the advantage of maintaining over several minutes (depending on the total injected volume) the enhancing effect of the agent.

**Correlation with Doppler flow wire.** The high agreement between intracoronary and transthoracic Doppler measurements relies on the high quality of spectral tracing obtained by enhanced TTE Doppler, and more important, because Doppler sampling by TTE Doppler was very likely performed in the post-stenotic segments as was Doppler flow wire. In fact, sampling by TTE Doppler was performed in all patients in the distal LAD segment. This makes it almost certain to be positioned in a post-stenotic segment in patients with proximal and mid-LAD stenosis. Post-stenotic CFR is much more accurate than prestenotic CFR in assessing residual vasodilatory capacity of the vascular bed subtended to a narrowed coronary artery (13). In fact, CFR measured in regions with branches proximal to the lesion is pseudo-normalized and, thus, is diagnostically unreliable because flow is concurrently assessed for regions of varying vasodilatory reserve, hence reflecting a weighted average of these potentially disparate zones. In a recent study (14) aimed at comparing CFR evaluated by TEE Doppler (a
technique that by definition is able to assess only prestenotic CFR because velocity recording is made in the proximal LAD with CFR measurements obtained with intracoronary Doppler flow wire in the post-stenotic segment, no correlation ($r = 0.181$) was found between the two methods.

In cases 1, 8, 10 bis and 15 bis (Table 2) transthoracic Doppler considerably underestimated or overestimated IDFW results. Case 1 overestimation by TTE Doppler is very likely explainable because CFR was probably assessed in a normal diagonal branch (stemming off the LAD before the 60% stenosis) instead of that in the distal LAD. This could rarely happen in patients with big diagonal branches leading to the left ventricular apex. Alternatively, but less likely, we could have sampled proximally to the stenosis. In case 8 bis the difference can be explained by different effects of dipyridamole on coronary microcirculation with respect to intracoronary adenosine. Dipyridamole, in fact, produces maximal hyperemia in a smaller percentage of patients than does intracoronary adenosine, assuming a papaverine effect as the reference maximal effect (9). In Patients 10 bis and 15 bis the overestimation of CFR by TTE Doppler can probably be justified by the fact that a certain recovery of CFR at the time of the transthoracic study (performed 24 h after revascularization and IDFW evaluation) might have taken place (15).

CFR measurement reproducibility. Short-term reproducibility of CFR measurement by enhanced transthoracic Doppler was very high (limits of agreement: $-0.3$ to $+0.3$) paralleling the reproducibility of IDFW (9). That this new method is reproducible is also supported by the agreement with a very reproducible method such as IDFW. In addition to the precision of the measurements, the noninvasiveness of this approach aids in keeping measurements repeatable. Thanks to its total noninvasiveness, in fact, our method does not alter per se hemodynamics (in particular, heart rate), thus not introducing an important source of variability of CFR measurements as previous studies have clearly demonstrated (16).

Transthoracic echo Doppler assessment of coronary flow and reserve. This study confirms and expands our preliminary data comparing CFR as assessed by this new method with a gold-standard method such as IDFW. In that previous experience, a small series of patients (16) was studied; furthermore, in accordance with our previous protocol, dipyridamole was used instead of adenosine. Adenosine, however, is a more powerful vasodilator that best suits our echo contrast administration protocol requirements thanks to its rapid action and favorable kinetics (17). Thus, in this last series a new approach with adenosine was adopted in all patients except the first seven enrolled, in which the old protocol using dipyridamole was still used.

Transthoracic ultrasound without enhancement has been attempted in the past to visualize distal LAD and in some studies also to record Doppler flow (18,19). However, the success rate in visualizing the artery and to record the flow was so low that CFR evaluation was not attempted. It is interesting to note that our precontrast feasibility data (6) parallel those of these reports.

Study limitations. Some methodologic or hemodynamic factors could have partially affected comparison of the methods: 1) transthoracic and intracoronary Doppler evaluations were not performed simultaneously for logistical reasons; 2) adenosine was administered via different routes (IV vs. intracoronary) and in seven patients dipyridamole was used during TTE Doppler evaluation instead of IV adenosine. Although it has been proved that both dipyridamole and IV adenosine provide almost the same effect in terms of coronary microcirculation dilation (20), this can account for individual discrepancies; 3) during IDFW study, diastolic blood pressure was slightly but significantly lower than during transthoracic Doppler study. Also, the heart rate significantly increased after IV adenosine, and it remained unchanged after intracoronary bolus (Table 1). However, these minor changes in hemodynamic conditions probably did not affect CFR, as previously demonstrated (16).

Some potential limitations of this new method need to be
discussed. First, blood flow velocity in a big diagonal branch leading to the apex could be erroneously considered as blood flow velocity in the distal LAD (Patient 1 in Table 2). Second, in CAD patients with distal lumen narrowing, prestenotic CFR can be assessed despite an attempt to measure flow velocity in the distal LAD. Third, CFR assessment can be invalidated if the noninvasive CFR measurement is performed at the stenosis site. In our study,

Table 2. Clinical, Angiographic Findings and CFR Values by Both IDFW and Enhanced TTE

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>TTE Drug</th>
<th>Clinical Findings</th>
<th>Stenosis Severity (%)</th>
<th>Location</th>
<th>CFR E-TTE</th>
<th>CFR IDFW</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Aden</td>
<td>MI</td>
<td>60%; mid</td>
<td></td>
<td>3.46</td>
<td>2.22</td>
</tr>
<tr>
<td>2</td>
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<td>MI</td>
<td>0%</td>
<td></td>
<td>3.60</td>
<td>3.55</td>
</tr>
<tr>
<td>3</td>
<td>Aden</td>
<td>Angina; Post-PTCA</td>
<td>40%; prox</td>
<td></td>
<td>2.79</td>
<td>2.86</td>
</tr>
<tr>
<td>4</td>
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<td>Angina</td>
<td>50%; mid</td>
<td></td>
<td>2.06</td>
<td>2.41</td>
</tr>
<tr>
<td>5</td>
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<td></td>
<td>3.24</td>
<td>3.29</td>
</tr>
<tr>
<td>6</td>
<td>Dip</td>
<td>Angina</td>
<td>70%; distal</td>
<td></td>
<td>2.07</td>
<td>2.24</td>
</tr>
<tr>
<td>7</td>
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<td>MI</td>
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<td></td>
<td>1.91</td>
<td>2.29</td>
</tr>
<tr>
<td>8</td>
<td>Dip</td>
<td>MI</td>
<td>40%; distal</td>
<td></td>
<td>3.64</td>
<td>4.25</td>
</tr>
<tr>
<td>9</td>
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<td>MI (pre-PTCA)</td>
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<td></td>
<td>1.33</td>
<td>1.67</td>
</tr>
<tr>
<td>9 bis</td>
<td>Dip</td>
<td>Post-PTCA</td>
<td>&lt; 20%; mid</td>
<td></td>
<td>3.05</td>
<td>3.54</td>
</tr>
<tr>
<td>10</td>
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<td>Angina (pre-PTCA)</td>
<td>70%; mid–60%; distal</td>
<td></td>
<td>2.02</td>
<td>2.09</td>
</tr>
<tr>
<td>10 bis</td>
<td>Aden</td>
<td>Post-PTCA</td>
<td>0%</td>
<td></td>
<td>1.83</td>
<td>1.28</td>
</tr>
<tr>
<td>11</td>
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<td>MI</td>
<td>0%</td>
<td></td>
<td>2.48</td>
<td>2.57</td>
</tr>
<tr>
<td>12</td>
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<td>Angina</td>
<td>40%; distal</td>
<td></td>
<td>4.35</td>
<td>4.42</td>
</tr>
<tr>
<td>13</td>
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<td>MI</td>
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<td></td>
<td>2.71</td>
<td>2.47</td>
</tr>
<tr>
<td>14</td>
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<td>Angina</td>
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<td></td>
<td>2.89</td>
<td>2.90</td>
</tr>
<tr>
<td>15</td>
<td>Dip</td>
<td>MI (pre-PTCA)</td>
<td>90%; mid</td>
<td></td>
<td>1.33</td>
<td>1.56</td>
</tr>
<tr>
<td>15 bis</td>
<td>Dip</td>
<td>Post-PTCA</td>
<td>20%; mid</td>
<td></td>
<td>3.26</td>
<td>2.80</td>
</tr>
<tr>
<td>16</td>
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<td>0%</td>
<td></td>
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<td>1.70</td>
</tr>
<tr>
<td>17</td>
<td>Aden</td>
<td>MI (pre-PTCA)</td>
<td>75%; prox –95%; mid</td>
<td></td>
<td>1.06</td>
<td>1.17</td>
</tr>
<tr>
<td>17 bis</td>
<td>Aden</td>
<td>Post-PTCA</td>
<td>30%; prox –0%; mid</td>
<td></td>
<td>2.06</td>
<td>2.29</td>
</tr>
<tr>
<td>18</td>
<td>Aden</td>
<td>Angina; MR</td>
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<td></td>
<td>1.72</td>
<td>1.58</td>
</tr>
<tr>
<td>19</td>
<td>Aden</td>
<td>MI</td>
<td>95%; mid</td>
<td></td>
<td>1.24</td>
<td>1.17</td>
</tr>
<tr>
<td>20</td>
<td>Aden</td>
<td>Angina</td>
<td>80%; distal</td>
<td></td>
<td>1.62</td>
<td>1.57</td>
</tr>
<tr>
<td>21</td>
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<td>3.11</td>
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<tr>
<td>22</td>
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<td>60%; distal</td>
<td></td>
<td>1.62</td>
<td>1.55</td>
</tr>
<tr>
<td>23</td>
<td>Aden</td>
<td>Angina</td>
<td>60%</td>
<td></td>
<td>2.28</td>
<td>2.18</td>
</tr>
<tr>
<td>24</td>
<td>Aden</td>
<td>MI (pre-PTCA)</td>
<td>70%; distal</td>
<td></td>
<td>1.66</td>
<td>1.46</td>
</tr>
<tr>
<td>25</td>
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<td>90%; prox</td>
<td></td>
<td>1.47</td>
<td>1.78</td>
</tr>
<tr>
<td>25 bis</td>
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<td>Post-PTCA</td>
<td>0%</td>
<td></td>
<td>3.26</td>
<td>3.00</td>
</tr>
</tbody>
</table>

Mean ± SD — — — 2.35 ± 0.87 2.36 ± 0.87

TTE drug = drug used to induce hyperemia during transthoracic Doppler study; Aden = IV adenosine; Dip = dipyridamole; E-TTE = enhanced transthoracic Doppler; IDFW = intracoronary Doppler flow wire; prox = proximal LAD segment; mid = mid-LAD segment; distal = distal LAD segment; LVH = severe left ventricular hypertrophy; MI = myocardial infarction; MR = severe mitral regurgitation; PTCA = percutaneous transluminal coronary angioplasty.

Figure 6. Scattergram (left panel) showing the relation between CFRs obtained by the same method (transthoracic Doppler) 1 h apart. Lines of equality (dotted line) and correlation (continuous line) are shown. Plot of the difference (right panel) between the two CFR measurements against their mean is shown. Dotted lines represent boundaries of mean ± 2 SD. Abbreviations as in Figure 3.
to circumvent this problem in patients with relatively high baseline velocity (>50 cm/s), possibly indicating acceleration at the stenosis site, a second Doppler sampling (reference value) was obtained in a different portion of the artery (7). Fourth, in a certain number of cases the theta angle was quite large (>30°), causing an 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 two velocities. Fifth, we measured a CFR index using a simple ratio of two velocities. This, however, as previously pointed out by others (21), is a reliable indicator of CFR.

Clinical implication. This completely noninvasive method to assess CFR has potentially interesting clinical applications. It may provide additional information to cardiac catheterization in the assessment of LAD coronary stenosis, especially those of intermediate anatomic severity whose functional influence, as indicated by previous observations (13), can be precisely assessed only with the post-stenotic CFR evaluation. It may also be useful in the assessment of the effect of PTCA procedure on the LAD either for early detection of restenosis or for monitoring CFR recovery modalities (15) (see Patients 10 bis and 17 bis in Table 2); in the noninvasive detection of LAD stenosis in situations such as in left bundle branch block, stress tests (both scintigraphy and echocardiography) are not reliable because of the high number of false positive studies; in assessing microcirculation impairment in conditions affecting CFR in the absence of CAD (see Patients 16 and 18 in Table 2); and because of the possible serial evaluation for exploring short- and long-term effects of various therapeutic interventions on CFR.

In conclusion, enhanced TTE Doppler closely agrees with IDFW in assessing CFR in the LAD. This new noninvasive method is feasible, reliable and reproducible in evaluating CFR in the LAD. Because of its noninvasive nature, this new method has a potential both in pathophysiologic and clinical studies. Larger studies are needed to investigate its potential in various diseases with possible CFR impairment.

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