Assessment of Flow Velocity Reserve by Transthoracic Doppler Echocardiography and Venous Adenosine Infusion Before and After Left Anterior Descending Coronary Artery Stenting

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OBJECTIVES	We sought to evaluate whether coronary flow velocity reserve (CFR) (the ratio between hyperemic and baseline peak flow velocity), as measured by transthoracic Doppler echocardiography during adenosine infusion, allows detection of flow changes in the left anterior descending coronary artery (LAD) before and after stenting.
BACKGROUND	The immediate post-stenting evaluation of CFR by intracoronary Doppler has shown mixed results, due to reactive hyperemia and microvascular stunning. Noninvasive coronary Doppler echocardiography may be a more reliable measure than intracoronary Doppler.
METHODS	Transthoracic Doppler echocardiography during 90-s venous adenosine infusion (140 μg/kg body weight per min) was used to measure CFR of the LAD in 45 patients before and 3.7 ± 2 days after successful stenting, as well as in 25 subjects with an angiographically normal LAD (control group).
RESULTS	Adequate Doppler spectra were obtained in 96% of the patients. Pre-stent CFR was significantly lower in patients than in control subjects (diastolic CFR: 1.45 ± 0.5 vs. 2.72 ± 0.71, p < 0.01; systolic CFR: 1.61 ± 1.02 vs. 2.41 ± 0.68, p < 0.01) and increased toward the normal range after stenting (diastolic CFR: 2.58 ± 0.7 vs. 2.72 ± 0.75, p = NS; systolic CFR: 2.43 ± 1.01 vs. 2.41 ± 0.52, p = NS). Diastolic CFR was often damped, suggesting coronary steal in patients with ≥90% versus <90% LAD stenosis (0.86 ± 0.23 vs. 1.69 ± 0.43, p < 0.01). Coronary stenting normalized diastolic CFR in these two groups (2.45 ± 0.77 and 2.64 ± 0.69, respectively, p = NS), even though impaired diastolic CFR persisted in three of four patients with ≥90% stenosis. Stenosis of the LAD was better discriminated by diastolic (F = 49.30) than systolic (F = 12.20) CFR (both p < 0.01).
CONCLUSIONS	Coronary flow reserve, as measured by transthoracic Doppler echocardiography, is impaired in LAD disease; it may identify patients with ≥90% stenosis; and it normalizes early after stenting, even in patients with ≥90% stenosis. (J Am Coll Cardiol 2001;38:155–62) © 2001 by the American College of Cardiology

Coronary stenting is becoming the most popular percutaneous intervention to treat coronary artery disease. Functional studies with intracoronary Doppler have demonstrated that stents that scaffold the arterial segment provide improved local flow conditions, as compared with balloon angioplasty (1).

Intracoronary Doppler is performed immediately after the intervention and may not reflect actual coronary flow reserve (CFR); it may underestimate CFR because of reactive hyperemia and microvascular stunning (2–4), or it may overestimate CFR in cases of early negative remodeling. In addition, intracoronary Doppler measures flow in large epicardial vessels, which have different compliance and flow dynamics, as compared with nutrient intramural vessels (5).

High-resolution transthoracic Doppler echocardiography (6) is a reliable method to assess CFR in the distal left anterior descending coronary artery (LAD) (7–12). At this level, epicardial flow closely reflects intramural flow, as demonstrated in basic experimental studies (5). Transthoracic Doppler echocardiography, performed in the days after LAD stenting, should overcome most of the limitations of intracoronary Doppler and may be used to monitor patients with stent implantation.

METHODS

Study group. We have studied 70 subjects: 45 consecutive patients (36 men and 9 women; age 62 ± 9 years [range 42 to 77]) with mid-proximal 60% to 95% LAD stenosis undergoing percutaneous coronary stenting and 25 consecutive subjects (18 men and 7 women; age 52 ± 9 years [range 31 to 65]) with angiographically normal LADs (control group). Exclusion criteria included anterior myocardial infarction, type 1 diabetes mellitus, left bundle branch block, degree II or III atrioventricular block, severe chronic obstructive pulmonary disease and bronchospasm. All patients were in sinus rhythm. All active coronary medications were withdrawn

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Abbreviations and Acronyms
ANOVA = analysis of variance
CFR   = coronary flow reserve
LAD   = left anterior descending coronary artery

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the day before the Doppler study. All subjects were informed of the purpose and nature of the study and provided written, informed consent before participation.

High-resolution transthoracic Doppler echocardiography. Echocardiography was performed, as previously described (13), with the patient or subject in the left lateral decubitus position, by using a multihertz transducer, allowing independent changes of frequency between two-dimensional (3.5 to 7.0 MHz) and color Doppler (3.5 to 6.0 MHz) imaging. The transducer was connected to an ultrasound system (Sequoia C256, Acuson, Mountain View, California), which utilizes multiple beam formers and coherent image formation, preserving both phase and amplitude data. To image the mid-distal LAD, the transducer was placed either at the cardiac apex or one intercostal space above, along the interventricular groove, and focused on the proximal field. Once an optimal two-dimensional image had been obtained, the transducer was rotated and tilted until one coronary segment could be visualized by color Doppler imaging. Color Doppler imaging was performed by reducing the Nyquist limit to 110 to 170 mm/s for 3.5 MHz, to 120 to 190 mm/s for 5 MHz and to 130 to 200 mm/s for 6 MHz. Adequate filtering was used to minimize low-frequency wall motion artifacts. Coronary flow velocity was sampled by pulsed Doppler echocardiography under a color-coding guide. The best long-axis view in color flow imaging was obtained to optimize the angle between the flow and Doppler beam. An angle >20° was avoided, and the theta angle was not corrected. The sampling site was marked on the chest and reported on paper to ensure post-stenting reproducibility. All studies were continuously recorded on half-inch S-VHS videotape for off-line analysis.

Coronary flow velocity reserve. Each patient or control subject underwent at least two Doppler recordings of LAD blood flow velocity at baseline and during short adenosine infusion (140 μg/kg body weight per min for 90 s). Patients underwent CFR assessment the day before and one to seven days after stenting, whereas control subjects had CFR assessment at 30-min intervals. The post-stent timing was chosen to avoid the influence of reactive hyperemia and microvascular stunning. All patients and control subjects had continuous heart rate and electrocardiographic monitoring. Blood pressure was recorded at baseline, during adenosine infusion and at recovery. Peak diastolic and systolic flow velocities were measured before and during adenosine infusion. Diastolic and systolic CFRs, defined as the ratio between hyperemic and baseline peak flow velocities, were calculated by the same operator performing the test (P.V.), who had no knowledge of the angiographic data.

Coronary intervention. Cardiac catheterization was performed in all patients by the percutaneous femoral approach. In patients undergoing stent implantation, ticlopidine, 250 mg twice a day orally, was administered, and 7,500 IU of heparin was given as a bolus at the beginning of the procedure. Additional heparin was administered to keep the activated clotting time $\geq$300 ms during the procedure. Elective stent deployment, with high-pressure balloon inflation, was preceded by balloon predilation in 30 patients, and the remaining 13 patients had direct implantation. Seven patients had multiple LAD stents. A total of 52 stents was used (37 ACS Tristar Multilink stents and 15 PenChant Biodivysio stents). Pre-procedural and post-procedural lumen diameter measurements were obtained on-line by electronic calipers. The outer diameter of the fluid-filled guiding catheter, which was centered, was used as a scaling device to obtain absolute arterial dimensions. Two orthogonal projections of the coronary artery lesion at end diastole were used to measure pre-procedural and post-procedural stenosis. The results of stenting were considered angiographically satisfactory on consensus of two experienced operators.

Feasibility and reproducibility of coronary reserve assessment. The feasibility of coronary imaging and Doppler recordings was evaluated by a consensus of two experienced observers. For each test, the three highest Doppler velocities were computed and averaged. To evaluate the effect of inter-observer variability on Doppler measurements, two independent, blinded observers (F.P. and P.V.) analyzed 17 randomly selected Doppler velocity recordings. To evaluate intra-observer variability, 20 randomly selected Doppler velocities were remeasured by the same operator (P.V.) one week apart. Inter-observer and intra-observer variabilities were calculated as the standard deviation of the differences between the two measurements or assessments, expressed as a percentage of the average value. To analyze intra-individual variability, baseline and hyperemic peak flow velocities of the two tests in control subjects were used, and the results of repeated measures analysis of variance (ANOVA) were considered.

Statistical analysis. Data are expressed as the mean value $\pm$ SD. Control subjects were studied with two tests repeated at 30-min intervals, whereas patients with LAD disease were studied before and after stent implantation. Two-factor ANOVA was used to test significance, with one factor being pre-stent versus post-stent implantation in patients with LAD disease (or corresponding phases in control subjects) and the other factor being patients with LAD disease versus control subjects. This model has two main effects (between and within) and an interaction. Two levels of each factor and three F statistics (each with 1 degree of freedom, with corresponding p values) were computed and reported. In the presence of a significant interaction, the physiologic interpretation is that the intra-time response in patients with LAD disease is different from that in control subjects. In the face of a significant interaction, it is common practice to ignore the main between and

Table 1. Coronary Doppler Velocities (Diastolic and Systolic) and Hemodynamic Data at Rest and Hyperemia in 24 Control Subjects and 43 Patients With LAD Disease

	Before	After	Control Subjects vs. Patients With LAD Disease (Between Effect)	Before vs. After (Within Effect)	Interaction
Peak flow velocity (cm/s)					
Diastolic					
Rest					
Control subjects	28 ± 9	27 ± 9			
LAD disease	31 ± 7	25 ± 6	0.06 (0.8024)	13.44 (0.0005)	10.75 (0.0017)
Hyperemia					
Control subjects	71 ± 16	70 ± 16			
LAD disease	43 ± 12	63 ± 17	28.58 (0.0000)	29.44 (0.0000)	32.58 (0.0000)
Systolic					
Rest					
Control subjects	17 ± 4	18 ± 3			
LAD disease	17 ± 6	14 ± 4	5.00 (0.0288)	2.60 (0.1120)	6.50 (0.0131)
Hyperemia					
Control subjects	41 ± 12	43 ± 9			
LAD disease	24 ± 11	33 ± 14	36.25 (0.0000)	6.75 (0.0116)	3.19 (0.0787)
Heart rate (beats/min)					
Rest					
Control subjects	74 ± 15	74 ± 15			
LAD disease	69 ± 9	69 ± 12	2.76 (0.1015)	0.17 (0.6854)	0.00 (0.9735)
Hyperemia					
Control subjects	83 ± 19	84 ± 19			
LAD disease	79 ± 12	76 ± 13	3.22 (0.0772)	0.54 (0.4632)	1.50 (0.2248)
Mean arterial blood pressure (mm Hg)					
Rest					
Control subjects	97 ± 7	98 ± 7			
LAD disease	99 ± 8	96 ± 7	0.02 (0.8776)	0.43 (0.5145)	9.81 (0.0026)
Hyperemia					
Control subjects	94 ± 5	94 ± 6			
LAD disease	89 ± 7	87 ± 7	14.51 (0.0003)	4.51 (0.0376)	2.37 (0.1289)

Before and after refer to study phases: at 30-min interval in control subjects; before versus after stenting in patients with left anterior descending coronary artery (LAD) disease. Two-factor analysis of variance was used to test significance, with one factor being before versus after stenting in patients with LAD disease (or corresponding phases in control subjects) and the other factor being patients with LAD disease versus control subjects. This model has two main effects (between and within) and an interaction. There are two levels of each factor and three F statistics (and corresponding p values) computed and reported. In the presence of a significant ($p < 0.05$) interaction, the physiologic interpretation is that the intra-time response in patients with LAD disease is different from the time response in control subjects. In the face of a significant interaction, it is common practice to ignore the main between and within effects. Pairwise comparisons are selectively reported in the Summary and omitted here for clarity. Data are presented as the mean value ± SD.

within effects. Pairwise comparisons using Bonferroni correction are given selectively. The same ANOVA model was used to analyze derived data (both diastolic and systolic CFR). One-way ANOVA was used to examine the control group versus the subgroups with <90% LAD stenosis versus ≥90% LAD stenosis. Categorical data were analyzed by using the corrected chi-square test. A p value <0.05 was considered statistically significant.

RESULTS

Stenting results. Coronary angiography showed a decrease in percent LAD stenosis, from 81 ± 10% before to 9 ± 3% after stent implantation.

Feasibility of coronary flow imaging. Technically adequate Doppler flow velocity tracings of the distal LAD were obtained before and after stenting in 43 (95.5%) of 45 patients with LAD stenosis and in 24 (96%) of 25 control subjects. The time required to perform the test was 12 ± 5 min (range 5 to 29). Low heart rate and favorable body build facilitated coronary imaging. Adenosine-induced hyperpnea was the main factor affecting flow velocity recordings, but it never prevented completion of the test.

Coronary Doppler echocardiography and hemodynamic data. Coronary Doppler velocities (diastolic and systolic), heart rate and mean arterial blood pressure at rest and during hyperemia in the study groups are shown in Table 1. A significant interaction in the two-factor ANOVA used was found for diastolic rest and hyperemic peak flow velocities, systolic rest peak flow velocity and rest mean arterial blood pressure.

Rest flow velocity. Rest peak diastolic flow velocity before stenting was slightly but not significantly higher in the
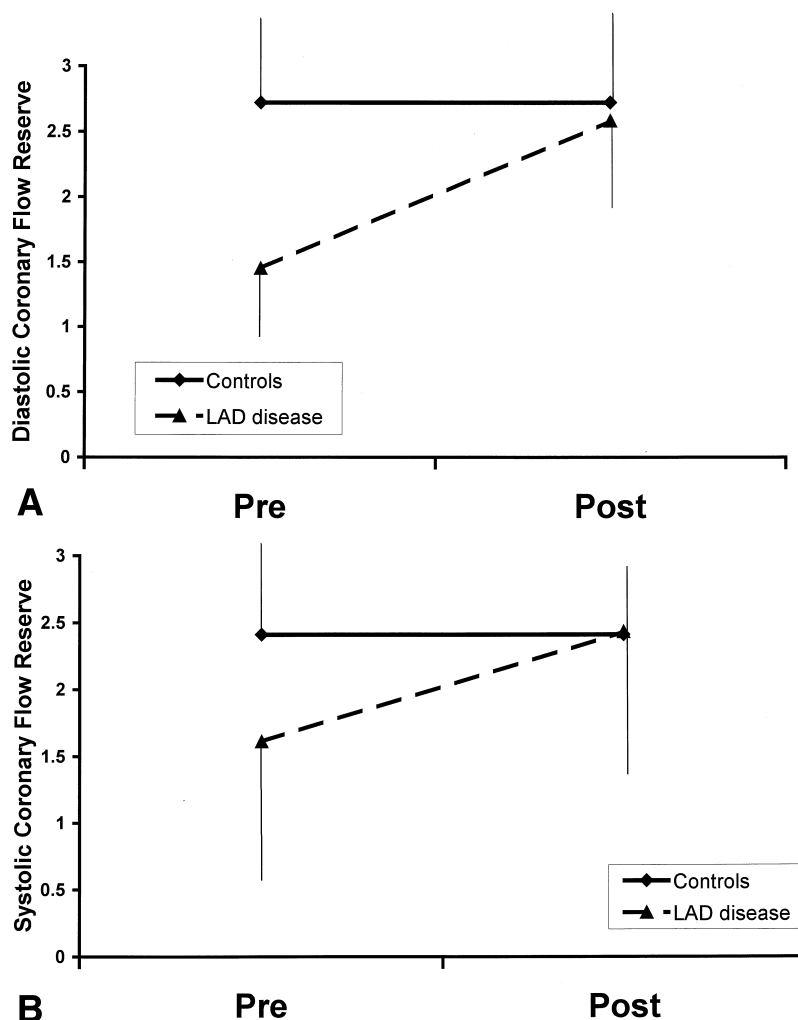
Figure 1. Diastolic **(A)** and systolic **(B)** coronary flow reserve (CFR) in patients and control subjects (see text for details). Note the steeper slope of the intra-time effect in patients with left anterior descending coronary artery (LAD) disease in the upper panel, who also present with the lower data dispersion both before and after stenting, meaning that diastolic CFR is more suitable than systolic CFR to index pre-stenting versus post-stenting Doppler results.

patients compared with the control subjects, and it significantly decreased after stenting. Rest peak systolic flow velocity also decreased after stenting, although not significantly (Table 1).
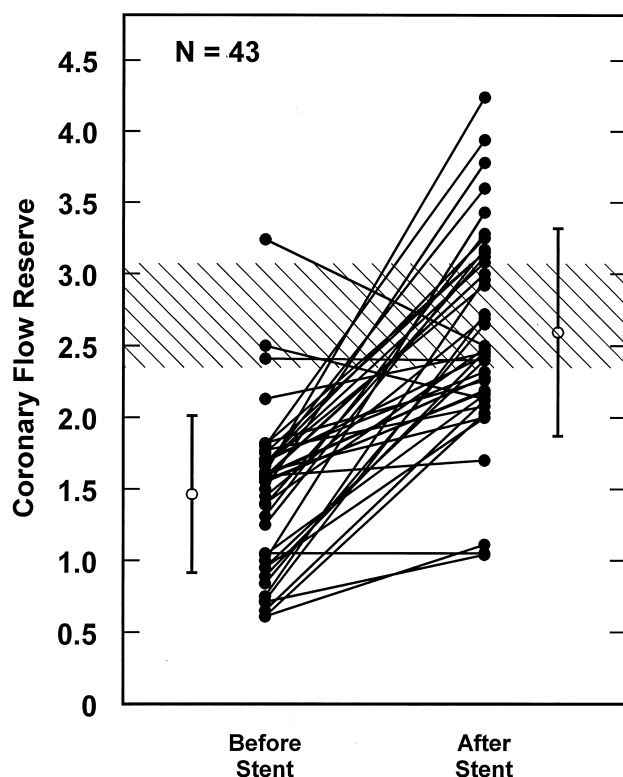
Flow reserve before and after stenting. Diastolic CFR was 1.45 ± 0.50 before and 2.58 ± 0.70 after stent implantation (Fig. 1A), approaching the reference values of control subjects (2.72 ± 0.71 in test 1 and 2.72 ± 0.75 in test 2). Systolic CFR was 1.61 ± 1.02 before and 2.43 ± 1.01 after stent implantation, which came close to the reference values of control subjects (2.41 ± 0.68 for test 1 and 2.41 ± 0.52 for test 2) (Fig. 1B). Two-factor ANOVA provided significant results for both diastolic and systolic peak flow velocities. However, the F statistics were larger for diastolic than for systolic peak flow velocity (20.93 vs. 4.71 for between term, 48.03 vs. 8.62 for within term and 47.57 vs. 8.37 for interaction term, respectively).

Stratification of patients with a diastolic CFR cut-off value <2.0 (abnormal) or ≥ 2.0 (normal) (7,9,10) correctly identified significant LAD stenosis in 39 (91%) of 43

patients before stenting and recovery of flow physiology in 39 (91%) of 43 patients after stenting (Fig. 2). All four patients with pre-procedural diastolic CFR ≥ 2.0 had mid-LAD stenosis (80% in 3 and 60% in 1). It is possible that in these patients, a Doppler recording was obtained close to the stenosis (14), producing paradoxical flow acceleration during adenosine infusion. Of the four patients with impaired post-stent diastolic CFR, three had severe LAD stenosis before stenting, with diastolic CFR ≤ 1.0, and one had intermediate LAD stenosis; none of these patients had a significant change in diastolic CFR after the procedure (Fig. 2).

Severe LAD stenosis. In 12 patients with severe ($\geq 90\%$) LAD stenosis, diastolic CFR was significantly lower than that in 31 patients with $<90\%$ LAD stenosis (0.86 ± 0.23 vs. 1.69 ± 0.43, $p < 0.0001$). Using a cut-off value of ≤ 1 for $\geq 90\%$ stenosis, 8 of 12 patients were correctly identified, whereas only 1 of 31 patients with $<90\%$ stenosis had diastolic CFR <1.0 (chi-square statistic $= 29.16$, $p < 0.0001$). However, this patient had a sequential 50% plus

Figure 2. Diastolic coronary flow reserve in patients with left anterior descending coronary artery disease before and early after stent implantation (p < 0.0001). Confidence intervals (95%) of the average value obtained in 23 consecutive control subjects provide a direct comparison to visually estimate how the variable distributes before and after the procedure. There is a clear overlap between the post-stent reserve distribution and average values measured in control subjects, indicating a high probability of normalized reserve after the procedure. Conversely, values measured before the procedure are far from normal in the large majority of patients.

but rapidly disappeared at the end of the infusion. Slight modifications in heart rate and arterial pressure were observed during drug infusion.

Observer and intra-individual variability. Inter-observer and intra-observer variability of Doppler velocity measurements were 3.2% and 2%, respectively. Intra-individual variability was excellent and never exceeded (in absolute average values) 2 cm/s for both diastolic and systolic peak flow velocity, which provided a maximal ±6% difference in relative terms.
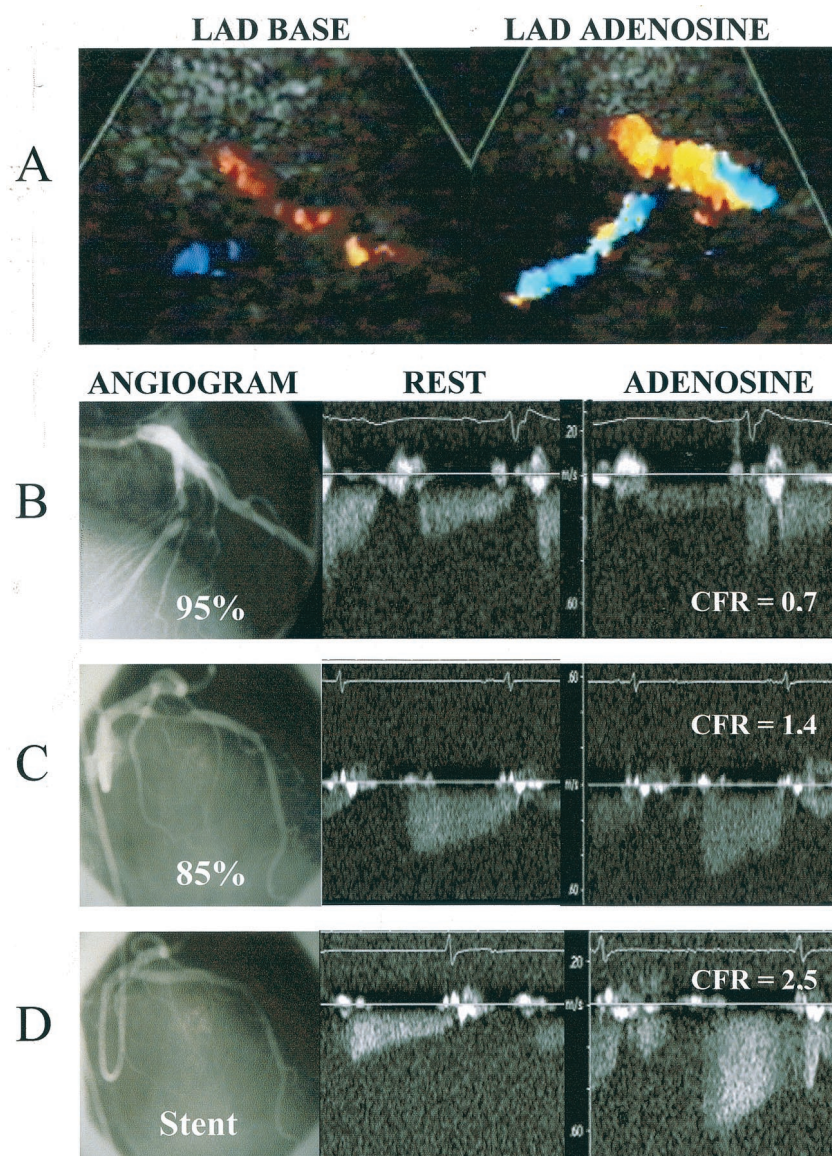
DISCUSSION

This study describes, for the first time, to our knowledge, the ability of transthoracic Doppler echocardiography to measure CFR changes in the distal LAD before and after successful stent implantation, and it demonstrates that CFR recovers toward the normal range early after the procedure.

Learning curve. In previous studies, the success rate in imaging the distal LAD ranged from 75% without a contrast agent to 100% with a contrast agent (6–13). The feasibility of adequate LAD visualization without a contrast agent increased in our experience from 75% in 1998 (6) to 96% in 2000, relegating the use of a contrast agent to ~5% of the patients.

Cost-effectiveness. Using the 90-s noncontrast approach of this study, the cost of the test for a patient weighting 70 kg is $20 (U.S.), which is 14 times less than the calculated $284 expense of the 7-min contrast-enhanced approach proposed by Caiati et al. (9). An alternative noninvasive technique is positron emission tomography, which is even more expensive and scarcely available (16–19).

Invasive versus noninvasive flow reserve assessment. Intracoronary Doppler has been introduced to optimize the results of percutaneous coronary interventions (1–4,20), but it has shown a surprisingly high rate of impaired CFR after balloon angioplasty (21,22) or stenting (50% and 30%, respectively), even in the absence of any residual angiographic stenosis (2–4). This phenomenon has been explained by two conflicting theories: microvascular stunning, where the microcirculation is not able to increase flow; or reactive hyperemia, where high post-ischemic baseline flow velocities mask a normal reserve. Invasive CFR is obtained after multiple balloon inflations, injection of contrast agent and administration of vasoactive drugs that may produce immediate post-procedural vasomotion instability (23–25). In addition, the influence of the guide wire or guiding catheter on the vascular endothelium and coronary flow dynamics is unpredictable. For these reasons, we have decided to measure CFR by transthoracic Doppler echocardiography in the first days after stenting. At this time, the influence of pharmacologic, metabolic, humoral or myogenic factors affecting coronary flow autoregulation is negligible, possibly explaining the lower rate of post-procedural impaired CFR of our study (4 [9.3%] of 43 patients) and of

80% LAD stenosis, producing an additive effect on flow dynamics (15). Stenting of the LAD equally normalized diastolic CFR in patients with and without severe stenosis (2.44 ± 0.77 and 2.64 ± 0.69, respectively; p = NS), but 3 of 12 patients with severe stenosis still had post-procedural impairment of flow (Fig. 2). Analysis of variance of three groups (control group and subgroups with <90% and ≥90% LAD stenosis) provided excellent discrimination for diastolic CFR (F = 49.30), whereas discrimination was lower for systolic CFR (F = 12.20), although both variables showed statistical significance (p < 0.00001). Figure 3 shows typical examples of angiography and rest and hyperemic Doppler echocardiography in a patient with severe LAD stenosis (Fig. 3B) and in another patient before and after successful stenting (Fig. 3 C and D).

Adenosine infusion. A maximal increase in coronary flow velocity was obtained within 60 s of drug infusion, and flow returned to baseline within 30 s of discontinuing the drug. No major adverse reactions occurred during or after adenosine infusion. Flushing, bradycardia, nausea, chest pain and headache were mild and transient. All patients experienced some degree of hyperventilation, which was marked in four,

Figure 3. (A) Increase in color Doppler signal intensity and velocity flow map during adenosine infusion. **(B)** Coronary angiogram of a patient with 95% stenosis of the left anterior descending coronary artery (LAD), and corresponding transthoracic rest and hyperemic Doppler velocities, with a damped diastolic coronary flow reserve (CFR) of 0.7 due to a decrease in peak diastolic velocity from 30 to 21 cm/s. **(C, D)** Pre-stenting and post-stenting coronary angiograms of a patient with 85% stenosis of the proximal LAD, and corresponding transthoracic Doppler velocities, with a diastolic CFR of 1.4 on the day before stenting **(C)**, increasing to 2.5 after the procedure **(D)**. Of note, the post-procedural increase in diastolic CFR is due to a reduction in rest and an increase in hyperemic velocity, as compared with pre-stenting values.

a previous positron emission tomographic report (19), compared with intracoronary Doppler (2–4). Of the four patients with persistently impaired reserve after stenting, three had severe LAD stenosis, suggesting exaggerated and persistent post-procedural peripheral vasoconstriction (26).

After stenting, we found a decrease in the post-procedural baseline velocity, although intracoronary Doppler showed the same pre-procedural and post-procedural baseline values (2). Coronary stenosis may induce flow acceleration or turbulence, or both, even at rest (14,27). After stent implantation, laminar flow may be restored (28) and velocities may reset toward normal reference values. Accordingly, recovery of CFR after successful stenting is related to normalization of both baseline and hyperemic

flow velocities, indicating that adequate lumen enlargement has been obtained and normal vascular conductance is restored.

Detection of severe stenosis. A couple of noninvasive Doppler studies have recently shown a difference in CFR between patients with intermediate and those with significant LAD stenosis (10,11), and a patient with 95% stenosis of the LAD and blunted CFR was anecdotally reported by Caiati et al. (9). In our study, we have consistently found CFR ≤ 1.0 in patients with severe LAD stenosis, suggesting coronary steal. This finding is in agreement with the experimental work of Gould et al. (29), who showed that hyperemia disappears at 88% to 93% vessel stenosis. If these results are confirmed in larger series, it will be possible to

noninvasively identify patients with severe LAD stenosis in whom recanalization is not deferrable.

Diastole or systole? Our study shows that systolic CFR follows the same behavior as diastolic CFR, but is less accurate for stratification of patients with LAD disease. However, three problems may affect systolic flow measurements: 1) nutrient myocardial flow occurs mainly in diastole, whereas systolic flow is essentially a capacitance flow (5); 2) systolic flow velocity varies greatly: it is anterograde in a large epicardial artery and retrograde in perforating branches, whereas in the watershed area, anterograde and retrograde flow may cancel each other out (5); and 3) systolic contraction may displace the coronary artery from the acoustic field, thus preventing true systolic velocity recording.

Nevertheless, some patients with severe stenosis show an abnormal increase in rest systolic flow velocity (Fig. 2). A larger series of patients is needed to investigate this aspect.

Adenosine infusion. Compared with other pharmacologic stress agents used for the detection of coronary artery disease, adenosine (30–32) has very fast action (~30 s) and washout (~10 s) times, allowing repetition of the test within minutes, just after flow velocity returns to baseline. The test is safe, cheap and repeatable and may last only 90 s, because the hyperemic response occurs within 30 to 60 s.

Study limitations. This study presents some limitations. First, we did not compare transthoracic with intracoronary Doppler. However, other investigators have validated the technique (8,10), and repeating catheterization on the first days after stenting to invasively measure CFR is not practical. Second, we did not consider the influence of hypercholesterolemia or other coronary risk factors on vasomotor tone, because the sample size of this investigation was too small. However, CFR was restored shortly after stenting in almost all patients, demonstrating the prominent role of releasing the preexisting coronary obstruction. Finally, only the LAD can be imaged consistently, whereas other coronary arteries, such as the posterior descending coronary artery, are currently under investigation (33).

Conclusions. Noninvasive Doppler echocardiography shows impaired CFR in patients with LAD disease and may identify severe stenoses. Shortly after stenting, CFR is restored, demonstrating early recovery of microvascular tone. This method shows the potential for detection of in-stent restenosis.

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