

Early Noninvasive Evaluation of Coronary Flow Reserve after Angioplasty in the Left Anterior Descending Coronary Artery Identifies Patients at High Risk of Restenosis at Follow-Up

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Background: Coronary restenosis is the most important clinical limitation after percutaneous coronary intervention (PCI), and coronary flow reserve (CFR) is reduced in the presence of significant coronary stenosis. This study evaluated whether detection of early reduction of Doppler echocardiographically derived CFR in the left anterior descending coronary artery can identify patients at high risk for developing restenosis after successful PCI.

Methods: Doppler echocardiographically derived CFR was studied in 124 consecutive patients at 1-month and 6-month follow-up after PCI in the left anterior descending coronary artery, together with coronary angiography.

Results: Restenosis was detected in 39 angiographic examinations (group A) and no coronary restenosis in the remaining 85 (group B) at 6 months. At 1 month, CFR was reduced in group A compared with group B ($P < .0001$), and a significant reduction of CFR in group A ($P < .0001$) but not in group B ($P = .89$) was detected at 6 months. $CFR \leq 2.5$ at 1 month was 67% sensitive and 87% specific for predicting significant restenosis, with positive and negative predictive values of 67% and 87%, respectively.

Conclusions: $CFR \leq 2.5$ detected 1 month after PCI in the left anterior descending coronary artery has the potential to identify patients at higher risk for developing coronary restenosis and indicates the need for close clinical follow-up. (J Am Soc Echocardiogr 2012;25:902-10.)

Keywords: Echocardiography, Coronary flow reserve, Restenosis, Coronary artery disease, Follow-up studies

Although the use of stents has reduced the angiographic incidence of restenosis after percutaneous coronary intervention (PCI),¹ it remains one of the major clinical problems,² occurring randomly and often unexpectedly a few months after PCI.^{3,4} In addition, although the recent introduction of drug-eluting stents has reduced the post-PCI restenosis rate, the need for longer monitoring for late restenosis or thrombosis has been suggested, especially in patients with “off-label” indications.^{5,6} Coronary flow reserve (CFR) and its derivative by means of Doppler flow wire have been used in the catheterization

laboratory to evaluate post-PCI results,⁷ showing only fairly good prediction of the restenosis rate at follow-up,⁸⁻¹⁰ probably because CFR was attained immediately after the procedure,^{8,11} at a moment when it may be temporarily impaired because of microvascular coronary dysfunction.^{10,12,13} The ability to identify patients who may need closer follow-up for restenosis may be particularly useful in an era of regional referral centers that perform coronary interventions. Moreover, because the issues of early recoil and microvascular dysfunction appear to be linked to increased risk for restenosis, 1-month evaluation may be a reasonable approach if done using a technique that is economically feasible. A method capable of monitoring CFR noninvasively and repeatedly after a sufficient time lapse from PCI would clearly be advisable to clarify the role of CFR in predicting the restenosis process in the long term. Doppler transthoracic echocardiography (TTE) allows the serial assessment of CFR, has been shown to follow intracoronary flow-derived data closely,¹⁴⁻¹⁷ and has been shown to be useful in detecting coronary restenosis after elective PCI in coronary artery disease^{18,19} as well as in monitoring coronary microcirculatory dysfunction.^{20,21}

We therefore sought to evaluate whether “early” (1-month) determination of noninvasive CFR by TTE is capable of predicting which patients are at higher risk for developing significant coronary restenosis after elective PCI during clinical follow-up.

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Abbreviations

CFR = Coronary flow reserve
CI = Confidence interval
LAD = Left anterior descending coronary artery
PCI = Percutaneous coronary intervention
TTE = Transthoracic echocardiography

METHODS

Patient Population

We studied 124 consecutive patients (92 men; mean age, 63 ± 9 years; age range, 38–80 years) with coronary artery disease, submitted to elective PCI on the left anterior descending coronary artery (LAD). They were enrolled in a multicenter study, from June 2001 to February 2005, conducted by

the Clinical Cardiology Unit at the University of Cagliari ($n = 64$) and the Cardiology Unit at the University of Genoa ($n = 60$). Patients enrolled in the study agreed to undergo follow-up angiography at approximately 6 months irrespective of symptoms.

Exclusion criteria included previous myocardial infarction in the LAD territory, total or functional coronary occlusion, grade II or III atrioventricular block, severe chronic obstructive pulmonary disease, and bronchospasm. Patients were not selected on the basis of good transthoracic Doppler signals; no patient was excluded for inadequate echocardiographic image quality. An institutional review committee approved the study, and all patients gave informed consent.

Follow-Up Protocol

All study patients underwent follow-up angiographic studies. Of the 124 follow-up studies, 20 were performed earlier than the initially scheduled time, because of new symptoms of typical angina ($n = 14$) and/or evidence of ischemia on routine noninvasive cardiac imaging tests (exercise stress test or dobutamine stress echocardiography; $n = 6$). The remaining 104 angiographic studies were performed at the scheduled time (6 ± 1 months after percutaneous transluminal coronary angioplasty). All patients had a median follow-up period of 6 months (range, 2–12 months). Over this time span, they underwent clinical evaluation and CFR assessment twice: early, approximately 1 month after the procedure (median, 1 month; range, 0.5–4 months), and late, about 6 months after the procedure (median, 6 months; range, 3–10 months). Coronary angiography was performed at the end of the follow-up period after elective PCI, 1 day after the late CFR assessment. The late assessment of CFR and coronary angiography were performed before the scheduled time, when new symptoms of typical angina and/or evidence of ischemia was found on routine noninvasive cardiac imaging tests (exercise stress test or dobutamine stress echocardiography). During follow-up, a new PCI procedure, at the previous PCI site, was performed if clinically indicated. All patients received bare-metal stents in the LAD, and a total of 148 stents (in 124 PCI procedures) were used. In particular, 77 patients had one stent delivered, 34 had two stents, and one had three stents, and balloon angioplasty alone was performed in 12 patients.

CFR Assessment

Echocardiography was performed for CFR evaluation with TTE, as previously described.^{15–18} Briefly, CFR was measured in the distal LAD, resulting in a modified foreshortened two-chamber view, with Doppler recordings of the basal flow, and during adenosine infusion at a rate of 0.14 mg/kg/min for 3 to 5 min. Cardiac medications were not interrupted before adenosine, although all medications or methylxanthine-containing substances were withheld 48 hours before the study. Beverages containing methylxanthine substances

(cola, tea, coffee, etc.) were restricted for 24 hours before the study. CFR in the LAD was calculated as the ratio of hyperemic to basal diastolic flow velocity (for each parameter, the highest of three cycles was averaged) by one experienced echocardiographer performing the test blinded to the angiographic and clinical data. Adenosine stress echocardiography was performed only to assess CFR; stress-induced left ventricular wall motion abnormalities were evaluated in different sessions with standard dobutamine stress echocardiography in each patient at follow-up of 1 and 6 months.

Coronary Angiography

Coronary angiography was performed according to the standard Judkins method with the femoral or radial artery approach, as indicated. Coronary stenosis was assessed from orthogonal angiographic projections by one investigator, unaware of the CFR results. Coronary restenosis in the LAD was defined as >50% luminal diameter narrowing at the previous PCI site on follow-up angiography assessed by quantitative coronary angiography. In addition, in patients with significant restenosis, we also used the classification of Mehran *et al.*²² to characterize in-stent restenosis: pattern I includes focal lesions (≤ 10 mm in length; 10 patients), pattern II includes in-stent restenosis (>10 mm; 12 patients), pattern III involves proliferative disease outside the stent restenosis (15 patients), and pattern IV is total occlusion restenosis (two patients). These data were matched with noninvasive CFR detected at 1-month and 6-month follow-up.

Statistical Analysis

Continuous data distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables with no skew are presented as mean \pm SD and skewed variables as medians and interquartile ranges. Student's *t* tests, analysis of variance, or Mann-Whitney tests (two sided) were used to compare continuous variables between groups. Differences between frequencies were assessed using χ^2 tests. Sensitivity, specificity, and positive and negative predictive values were determined according to standard definitions. Both the relationship between CFR and quantitative coronary angiography and between CFR and the Mehran classification were evaluated using Spearman's nonparametric test and expressed as ρ coefficients. Angiographic evidence of restenosis was considered the positive reference standard. Receiver operating characteristic curve analysis was performed to test the predictive discrimination of patients with or without restenosis. A manual Cox regression model with backward elimination was performed on blocks of variables until a regression model with only significant or marginally significant ($P < .10$) variables was obtained; the independent predictive values of selected covariates were then evaluated. *P* values $< .05$ were considered significant. Data were analyzed using SPSS version 18.0 (SPSS, Inc., Chicago, IL).

RESULTS

All 124 patients who were initially enrolled in the study underwent angiographic studies at follow-up. Of the 124 follow-up studies, 20 were performed earlier, before the initially scheduled time, because of new symptoms of typical angina ($n = 14$) and/or evidence of ischemia on routine noninvasive cardiac imaging tests ($n = 6$); 12 of these 20 patients showed coronary restenosis caused by severe in-stent endothelial proliferation. The remaining 104 angiographic studies were performed at the established end of follow-up (6 ± 1 months

Table 1 Baseline characteristics of patients

Variable	Group A (restenosis*) (n = 39)	Group B (no restenosis†) (n = 85)	P
Age (y)	64.3 ± 8.9	62.7 ± 9.6	.40
Men	35 (90%)	58 (68%)	.014
Systolic blood pressure (mm Hg)	139.8 ± 16.2	134.4 ± 18.5	.12
Diastolic blood pressure (mm Hg)	85 ± 8.3	82.2 ± 11.9	.20
Heart rate (beats/min)	65.1 ± 12.3	69.1 (14.4)	.14
Family history of CAD	12 (31%)	33 (39%)	.54
Total cholesterol >6.5 mmol/L	21 (54%)	57 (67%)	.22
Diabetes mellitus	3 (8%)	13 (15%)	.39
Statin use	31 (79%)	66 (78%)	.81
Hypertension	23 (59%)	59 (69%)	.31
Cigarette smoking	21 (54%)	24 (48%)	.33
Number of vessels > 1	19 (49%)	41 (48%)	.60
Angina at 1-month follow-up	3 (8%)	11 (13%)	.54
Angina at 6-month follow-up	21 (54%)	13 (18%)	<.001

Data are expressed as mean ± SD or as number (percentage).

*Greater than 50% on quantitative coronary angiography at 6-month follow-up.

†Less than or equal to 50% on quantitative coronary angiography at 6-month follow-up.

after PCI). At follow-up, coronary angiography revealed significant coronary restenosis (luminal narrowing > 50%) in 39 angiographic examinations (31.5%; group A) and none in the remaining 85 (68.5%; group B).

Clinical Findings

Among the clinical and demographic findings, angina become significantly more frequent in the restenosis group, with early CFR ≤ 2.5, in late follow-up (54% vs 18%, $P < .0001$). The other variables, such as age, diabetes, hypertension, hypercholesterolemia, smoking habit, and the use of statins, did not differ in the two groups (Table 1).

Hemodynamics

There were no significant differences in heart rate, systolic and diastolic aortic pressure, or angiographic variables, in terms of number of vessels involved, in either patient group (Table 1).

CFR at 1-Month Follow-Up

Pulsed-wave Doppler tracings, suitable for CFR evaluation, were obtained in the distal portion of the LAD in all patients. CFR studies were well tolerated by all subjects. Wall motion during stress echocardiography was normal in all patients. In the entire study population, there was an inverse relationship between CFR detected at 1 and 6 months and the grade of coronary restenosis expressed by quantitative coronary angiographic values at follow-up ($P < .0001$, $\rho = -0.47$, and $P < .0001$, $\rho = -0.69$, respectively; Figure 1).

At baseline, peak diastolic velocity in the LAD was similar in the two groups (median, 31 cm/sec [interquartile range, 23–43 cm/sec] vs 27 cm/sec [interquartile range, 23–32 cm/sec]; $P = .12$). However, during hyperemia, flow velocity increased more in group B than in group A (86 ± 27 cm/sec vs 73 ± 31 cm/sec, $P = .03$). Figures 2 and 3 show a representative example. Consequently, CFR was significantly reduced in group A at 1-month follow-up (2.3 ± 0.65 vs 3.1 ± 0.69 , $P < .0001$; Figure 4). A cutoff value of ≤ 2.5 at 1 month was identified as optimal by receiver operating characteristic curve analysis (area under the curve, 0.79 ± 0.05 ; 95% confidence interval

[CI], 0.70–0.88; $P < .0001$) for the best prediction of the occurrence of restenosis at the previous PCI site at follow-up (Figure 5). On the basis of this cutoff, the event rate and calculated relative risk for coronary restenosis were both much higher in the group with lower (≤ 2.5) than with higher (> 2.5) CFR (67% vs 15%, $P < .0001$). The probability of coronary restenosis was > 10 times higher in patients with lower CFR than in those with higher CFR (odds ratio, 11; 95% CI, 4.5–26.9; $P < .0001$). Detection of low CFR at 1 month (CFR at 1 month ≤ 2.5) was the only independent risk factor of restenosis (hazard ratio, 4.2; 95% CI, 2.1–8.2; $P < .0001$). Male gender was only a marginally significant risk factor (hazard ratio, 2.4; 95% CI, 1.16–6.8; $P = .09$) (multivariate model $\chi^2 = 24.496$, $P < .001$).

CFR ≤ 2.5 at 1 month was 67% sensitive and 87% specific for detecting significant restenosis, with positive and negative predictive values of 67% and 87% respectively, and accuracy of 79%. Moreover, in the restenosis group, CFR at 1 month decreased significantly, with an increase in in-stent restenosis, according to the Mehran classification (pattern I, 2.64 ± 0.5 ; pattern II, 2.3 ± 0.6 ; pattern III, 2.2 ± 0.6 ; pattern IV, 1.15 ± 0.2 ; $P = .023$), and there was an inverse relationship between CFR detected at 1 month and the Mehran classification ($P < .05$, $\rho = -0.32$; Table 2).

Time Course of CFR Over 6 Months

As expected, CFR at 6-month follow-up was more predictive of coronary anatomy, because it was performed close to the angiographic evaluation (the day before), resulting in higher sensitivity (94% vs 67%, $P = .0001$) and almost the same specificity (85% vs 87%, $P = .90$) than the test performed at 1 month. CFR also showed a variation pattern over time that was significantly different in the two groups: in group A, CFR became worse (from 2.3 ± 0.65 to 1.63 ± 0.48 , $P < .0001$), and a negative Δ value of ≥ 0.5 was significantly more frequent than in group B (55% vs 28%). In group B, CFR did not change during follow-up (from 3.1 ± 0.68 to 3.08 ± 0.88 , $P = \text{NS}$). There was an improvement in CFR, with a Δ value of ≥ 0.5, in 22 patients (19%) in group B ($P = .0001$), but there was no improvement in group A (Figure 4). In 13 patients in group B, suboptimal CFR was found at 1 month, and in three patients, low CFR persisted at 6 months, although

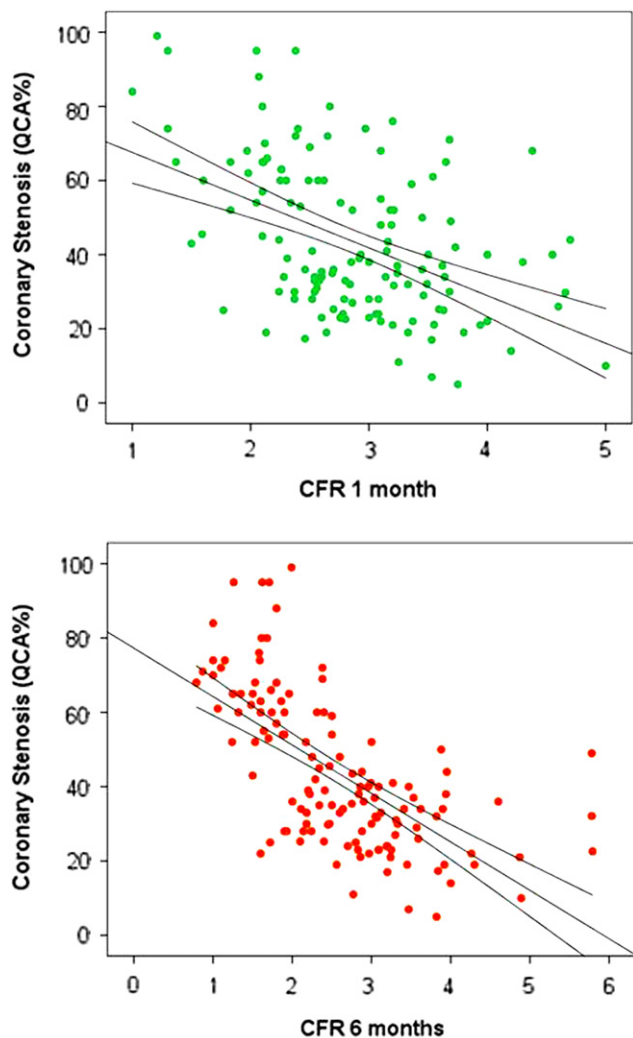


Figure 1 Relationship between CFR monitored at 1 month and coronary restenosis (quantitative coronary angiography [QCA]) at 6-month follow-up ($P < .0001$, $\rho = -0.47$) (top) and between CFR monitored at 6-month follow-up and coronary restenosis (QCA) at 6-month follow-up ($P < .0001$, $\rho = -0.69$) (bottom).

without restenosis; there was an improvement in the other 10 patients ($P = .49$; Figure 5). Among patients with $CFR > 2.5$ at 1 month ($n = 85$), 11 had severe reductions of $CFR (< 2)$, of whom nine had restenosis at follow-up angiography and only four had angina.

DISCUSSION

This study shows that CFR, assessed noninvasively at early follow-up (about 1 month after PCI), has the potential to identify patients at high or low risk for coronary restenosis at late (6-month) follow-up (restenosis rates of 67% and 15%, respectively, $P < .0001$), with a CFR threshold value of 2.5.

Usefulness of Noninvasive Monitoring of CFR Impairment after PCI

The measurement of intracoronary CFR to assess the effect of PCI on coronary stenosis and to predict major clinical complications in follow-up has been explored in the past,^{8-11,13,23-25} with evidence

of the more frequent incidence of major adverse coronary events in patients with suboptimal CFR immediately after PCI.^{25,26} Nevertheless, invasive CFR assessment has not been successful in predicting patients with restenosis in clinical follow-up.⁸

Our study indicates that in the group of patients with $CFR \leq 2.5$ detected 1 month after PCI, there was a higher incidence of significant coronary restenosis in follow-up, probably because CFR was attained at a point when microvascular recovery after PCI occurs, thus allowing better correspondence between coronary morphologic data and functional parameters of coronary physiology such as absolute CFR. In addition, although there was a significant correlation between CFR values and the extent of coronary restenosis as assessed by quantitative coronary angiography (Figure 1), only patients with suboptimal CFR early after PCI had significantly higher incidence of angina during follow-up, as has been pointed out in other studies.¹¹ This may be due to the fact that although in-stent restenosis is a process that progresses markedly between 1 and 3 months after PCI and reaches a plateau thereafter,³ there is a consistent delay with respect to the clinical manifestation of myocardial ischemia: only about 50% of patients show important clinical symptoms related to angiographic restenosis.²⁷ Moreover, inducible ischemia, evaluated by exercise stress testing, myocardial perfusion imaging, or stress echocardiography, often cannot detect restenosis during the first month after PCI.²⁸ Conversely, impairment of CFR in the first few months after PCI detected by TTE may be capable of predicting the development of significant coronary restenosis at 6 months. This means that early absolute CFR quantitatively measures the functional significance of a coronary restenosis not severe enough to cause symptoms and/or stress-induced ischemia but still capable of reducing maximal hyperemic flow.²⁹

Importance of Time Delay in Assessment of CFR Impairment after PCI

Abnormal CFR can be detected in some patients immediately after PCI, even after optimal enlargement of the coronary vessel.¹³ This finding has been related to various mechanisms, such as high basal coronary flow velocities^{11,13} due to enhanced coronary flow caused by plaque microembolization³⁰ or increased microvascular resistance, or temporary microvascular coronary impairment with slow recovery after PCI.^{10,12,13}

In our study, basal coronary flow velocities were in the normal range and did not differ between the two subgroups of patients (with and without restenosis) both at 1-month and 6-month follow-up. These findings are similar to those of Piek *et al*,¹⁰ who found low basal coronary velocities in patients with reduced CFR immediately after PCI, although no significant increase in restenosis rate was detected in follow-up. In our opinion, this may be due to the different temporal evaluation of CFR after PCI performed in our study. In fact, noninvasive CFR assessment with TTE can be performed at a programmed time lapse after PCI, when functional impairment of the microcirculatory response is less important, because the coronary healing process is better achieved,³¹ thus avoiding the detection of persistently low CFR related to iatrogenic microvascular impairment, even after optimal PCI.¹⁹ In addition, the absence in our patients of previous myocardial infarction in the target vessel area excluded persistent impairment of the microcirculatory vasodilatory response and suggests that CFR reduction monitored with TTE during follow-up may be due to the lack of an appropriate hyperemic response due to true coronary restenosis of the vessel.

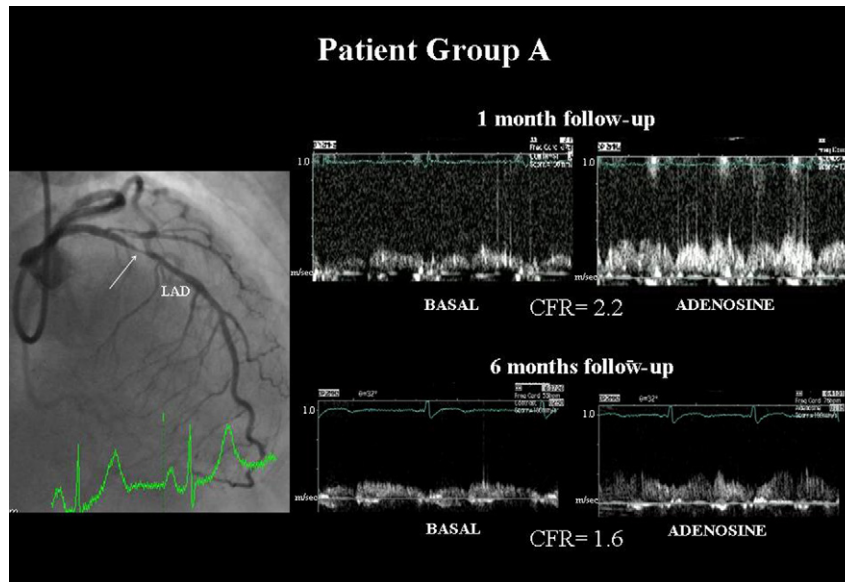


Figure 2 Example of a patient of group A who showed significant coronary in-stent restenosis at follow-up angiography (6 months after elective PCI). The patient had impaired CFR at 1 month (*top right*) and significant worsening at 6-month follow-up (*bottom right*). White arrow (*left*): in-stent restenosis seen at follow-up angiography.

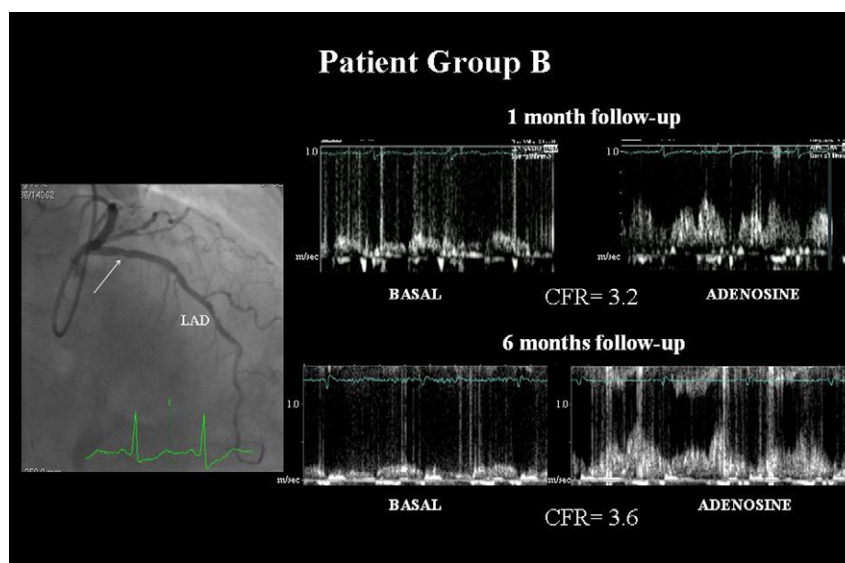


Figure 3 Example of a patient in group B with very mild, nonsignificant in-stent restenosis (<50%) at follow-up angiography (6 months after elective PCI). The patient had normal CFR at 1 month (*top right*) and a stable CFR value, with slight improvement, at 6-month follow-up (*bottom right*). White arrow (*left*): stent positioned in proximal LAD seen at follow-up angiography.

Clinical Usefulness of Noninvasive Assessment of Progressive CFR Impairment

The progression of restenosis after stent implantation may be due to various responses of the vessel to media injury, related to mechanical stress in the vessel, which appears to be independent of the “optimal” size of that vessel after PCI.³² Although most of the restenosis process occurs in the first 6 months after PCI,^{3,4} there is increasing evidence that an intermediate regression phase may be followed by renarrowing about 4 years later.³³ Our study showed that a noninvasive CFR value of ≤ 2.5 could be used to identify patients at risk for restenosis during 6-month follow-up. Moreover, all patients who showed a greater incidence of restenosis after PCI (group A) not

only had suboptimal CFR (≤ 2.5) at 1 month but also showed progressive worsening during follow-up, in comparison with patients with normal CFR at 1 month (group B), in whom no change was found (Figure 4).

Our study was not designed to investigate the mechanisms responsible for restenosis and reduced CFR in patients after PCI; nevertheless, some suggestions can be made.

Vessel restenosis after PCI seem to be the result of complex and primitive vascular “healing” response to injury,³⁴ which can be related to three major interrelated causes: vessel recoil with remodeling, haemostatic activation with thrombus formation, and neointimal growth. In particular, elastic recoil and remodeling can produce

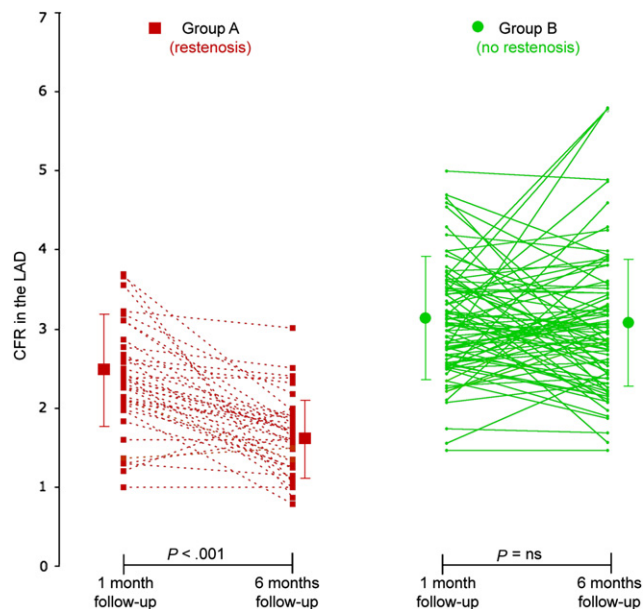


Figure 4 Individual-value bar graphs showing CFR values at 1 and 6 months for group A (left) and group B (right); in both graphs, direction of change is shown by lines connecting data. Mean \pm SD values are also shown.

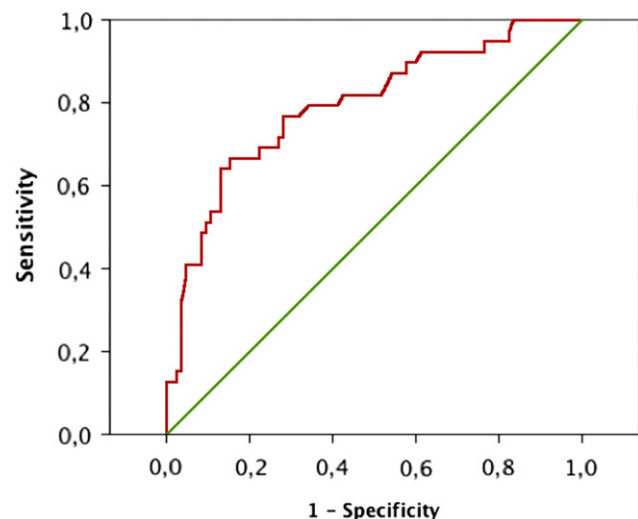


Figure 5 Plot of sensitivity against 1 minus specificity of CFR (receiver operating characteristic curves) in predicting angiographic restenosis at previous PCI site at 6-month follow-up.

growth factors that stimulate smooth muscle cells,³⁵ causing a narrowing of the vessel and a reduction of CFR values. Other clinical variables related to the severity of CAD, such as multivessel disease with a wide extension and diffusion of atherosclerosis, can reduce CFR even in a “normal” coronary angiography.³⁶ Also, in the presence of additional microvascular disease, CFR can remain low even after successful stent implantation.²³ Finally, because the arterial response to endothelial injury after PCI is directly related to an adequate coronary flow velocity, which affects endothelial shear stress,³⁷ an early impairment of CFR could increase the risk for neointimal hyperplasia and in-stent restenosis.

Thus, our study suggests that an evaluation of CFR, which is relatively inexpensive, simple, suitable for serial testing and is not limited by concurrent medication use,³⁸ can be helpful in patients with single-vessel disease also of intermediate severity.³⁹ If a normal value (>2.5) is found within 1 month after elective percutaneous transluminal coronary angioplasty, the risk for restenosis is low, and a conservative follow-up strategy would be appropriate. On the other hand, if a low value is detected (<2.5) a prompt and careful CFR study follow-up is mandatory, considering also the use of other imaging tests, and if a progressive reduction of CFR develops in the follow-up, the need to perform repeat cardiac catheterization should be taken into consideration. It is especially important to monitor patients who received medicated stents, in whom the need for longer monitoring for late restenosis or thrombosis has been suggested.^{5,6}

Limitations

This study had some limitations. First, impairment of absolute CFR may not be a pure expression of epicardial restenosis, but may also be influenced by microvascular and diffuse epicardial disease. This may explain the low CFR in the absence of angiographic restenosis in our series of patients. However, microvascular-mediated severe impairment of CFR should not be considered a frequent event, especially if, as in our study, it is possible to exclude major microvascular dysfunction, either anatomically mediated (previous large anterior myocardial infarction, signs of distal embolization during PCI procedure as confirmed by clinical assessment, creatine kinase-MB enzymes, electrocardiographic changes or echocardiographic kinetic abnormalities) or essentially functionally mediated (immediate post-PCI coronary microcirculatory stunning). It is more probable that in our patients, endothelial-mediated microcirculatory dysfunction (due to diabetes, hypertension, dyslipidemia or smoking; see Table 1) took place. Therefore, only mild worsening of CFR would be expected, because adenosine’s vasodilating effect is due to both an endothelium-dependent mechanism (30% of its total effect, indirectly mediated by the increase of shear stress) and an endothelium-independent mechanism (60%–70% of its total effect, by directly stimulating purinergic receptors of the microvascular smooth cells); the latter, more prominent effect takes place also in the presence of endothelial dysfunction.⁴⁰

Relative CFR and fractional flow reserve are more lesion specific parameters^{41,42}; relative CFR in particular requires as a theoretical assumption a uniform function of the whole microvascular bed and a normal reference artery. However, until now, both have been attained only invasively and thus are not suitable for serial studies. Conversely, acceleration of flow at the stenosis site is theoretically lesion specific⁴³ and can be measured with a noninvasive enhanced Doppler method over the entire LAD, as recently demonstrated.⁴⁴ Therefore, in cases of CFR impairment with doubtful mechanism, mild or no acceleration at the level of the balloon-treated artery may indicate a microcirculatory disease, whereas significant acceleration ($>82\%$ of the reference value)⁴⁴ would indicate epicardial restenosis. Accordingly, this combined approach (CFR and flow mapping) has the potential to discriminate the causes of absolute CFR impairment in post-PCI patients noninvasively.

Second, at the present time, CFR evaluation using TTE can be achieved with a feasibility reaching 100% only in the LAD,¹⁵⁻¹⁷ whereas the right coronary territory has lower feasibility,⁴⁵ and the circumflex artery is still not amenable to reliable study.

Table 2 Patient characteristics related to Mehran classification

Variable	Mehran classification of in-stent restenosis (n = 39)				P
	Pattern I (focal) (n = 10)	Pattern II (in-stent) (n = 12)	Pattern III (proliferative) (n = 15)	Pattern IV (Total occlusion) (n = 2)	
Age (y)	64 ± 7	63.5 ± 8.2	66 ± 10	58 ± 18.4	.60
Men	10	9	14	2	.22
Diabetes	1	0	1	1	.11
Hypertension	5	8	9	1	.80
Hypercholesterolemia	6	7	8	0	.45
Cigarette smoking	6	5	8	2	.45
Implanted stents/lesion	1.2 ± 0.4	1.4 ± 0.5	1.2 ± 0.4	1 ± 0	.60
Stent diameter (mm)	3 ± 0.33	3.1 ± 0.3	3 ± 0.4	2.5 ± 0	.16
Stent length (mm)	20 ± 7.8	18.1 ± 6.4	15 ± 5.4	11.5 ± 5	.18
Mehran	25.6%	30.8%	38.5%	5.1%	
Quantitative coronary angiography (%)	55.8 ± 3.9	69 ± 14.6	68.7 ± 10.4	90 ± 8	.001
CFR at 1 month	2.64 ± 0.5	2.3 ± 0.6	2.3 ± 0.6	1.15 ± 0.21	.023
CFR at 1 month ≤ 2.5	50%	66%	73%	100%	.46
CFR at 6-month follow-up	2.0 ± 0.6	1.7 ± 0.3	1.4 ± 0.4	1.31 ± 0.4	.03

Data are expressed as mean ± SD, as numbers, or as percentages.

Third, CFR assessment may be invalidated if measurements are performed at the coronary stenosis site¹⁵ or if the LAD is totally occluded, although accurate LAD mapping and preliminary knowledge of the patient's previous coronary anatomy, possible in this particular clinical context, can avoid these limitations.

Moreover, only creatine kinase-MB myocardial enzymes were monitored after PCI. Systematic determination of troponin enzymes was not performed to ascertain whether any microvascular damage had occurred because of the procedure (e.g., plaque microembolization) that could affect CFR determinations, although no periprocedural complications, electrocardiographic changes, or echocardiographic kinetic abnormalities were observed in any patient.

The study showed a relatively high restenosis rate (31%) in the cohort of patients. This could be related to the fact that a cutoff limit of 50% was used, and many patients were classified in the restenosis group, even though they had a mild restenosis rate (e.g., 52%–54%) at quantitative coronary angiographic measurements. Furthermore, the relatively high incidence of restenosis in our group could be linked to the comparatively small sizes of the coronary arteries in vessels with reference diameters < 3.0 mm, found in many of the patients.^{46,47}

Some patients had late referrals to our research clinics, resulting in wide variation in the time interval to the first CFR follow-up evaluation. Although this may represent a technical limitation of our protocol, we think this factor did not affect the physiologic meaning of the findings or the results of the study.

Last, our study was not designed to investigate the pathophysiology or the causes responsible for early reduction of CFR in patients after PCI. In this setting, future studies should be designed to understand the possible relationship between biologic mechanisms responsible for restenosis⁴⁸ and the reduction of noninvasive CFR during follow-up of patients after PCI.

CONCLUSIONS

The present study shows that noninvasive CFR assessment in the LAD by TTE performed at 1 month after PCI has the potential to

detect at an early stage patients who will probably develop restenosis at 6-month follow-up and thus require close monitoring. Further studies on a larger scale, eventually multicenter, are needed to confirm these preliminary data.

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