Frequency and Clinical Significance of Myocardial Ischemia Detected Early After Coronary Stent Implantation

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A high number (30%–50%) of reversible defects have been detected early after coronary balloon angioplasty. Inadequate luminal enlargement despite a good angiographic appearance has been suggested as a possible mechanism of these perfusion abnormalities, and some reports have shown better coronary flow reserve after coronary stent implantation than after balloon dilatation. The primary objective of this study was to evaluate the frequency of early ischemic defects detected by maximal exercise (plus dipyridamole) with ^{99m}Tc-tetrofosmin SPECT after successful coronary angioplasty with stent implantation. A secondary objective was to determine the prognostic value of these early ischemic defects. **Methods:** Thirty patients without previous myocardial infarction who successfully underwent 1-vessel coronary angioplasty with stent implantation were studied. Maximal-exercise ^{99m}Tc-tetrofosmin myocardial SPECT, with simultaneous dipyridamole if exercise was suboptimal, was performed at 6 ± 1 d (mean ± SD) after percutaneous transluminal coronary angioplasty. At 8 ± 3 mo, all patients were followed up clinically, and 77% of them underwent follow-up angiography. **Results:** The percentage of stenosis decreased from 68.5% ± 12.6% of luminal diameter to 9.3% ± 8.8% after stent implantation, and minimal luminal diameter increased from 0.89 ± 0.36 mm to 2.85 ± 0.45 mm. Mild-to-moderate reversible myocardial defects in the territory of the dilated artery were detected in 5 patients (17%), with no angiographic or procedural differences occurring between them and patients without ischemic defects. At follow-up, the target lesion revascularization rates depending on the presence or absence of early ischemic defects were 40% and 8%, respectively ($P = 0.18$). Angiographic restenosis occurred in 3 of 4 patients who had early ischemic defects and underwent follow-up angiography and in 3 of 19 patients who had no early ischemic defects and underwent follow-up angiography (restenosis rate, 75% and 16%, respectively; $P < 0.05$). **Conclusion:** Coronary angioplasty with stent implantation is associated with a 17% rate of ischemic defects early after the procedure. Patients with early myocardial perfusion defects after coronary stent implantation had a high rate of restenosis.

Key Words: coronary disease; stents; perfusion imaging

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A high incidence (30%–50%) of early ischemic defects after successful coronary balloon angioplasty has been reported (*1–7*). The delayed recovery of some of these perfusion abnormalities suggests that a transient defect in distal vessel autoregulation or a local spasm of the artery wall at the site of the dilatation is a possible mechanism of these early myocardial defects (*8,9*). However, studies have shown that in spite of a good angiographic appearance after balloon angioplasty, an inadequate result as detected by intravascular sonography could explain some of these perfusion abnormalities early after percutaneous transluminal coronary angioplasty (PTCA), and their presence has been associated with a high risk of restenosis and clinical events at follow-up (*10,11*). Coronary stent implantation has improved immediate angiographic results and reduced the restenosis rate (*12,13*). Preliminary reports have suggested that the larger residual luminal area obtained after stent implantation results in a better coronary blood flow than that obtained after balloon angioplasty (*14,15*). However, the incidence of early ischemic defects after coronary stent implantation and their relationship with restenosis have not been studied.

The primary objective of this study was to evaluate the incidence of early ischemic defects detected by simultaneous maximal subjective exercise (plus dipyridamole if exercise was insufficient) and ^{99m}Tc-tetrofosmin SPECT after optimal PTCA with stent implantation. A secondary objective was to determine the value of detecting early ischemic defects after coronary stent implantation in the prediction of late restenosis and clinical events.

MATERIALS AND METHODS

Patients

We included 30 consecutive patients who underwent successful 1-lesion PTCA with stent implantation. We knew before PTCA that all patients had myocardial ischemia, because functional testing had shown that positive findings or spontaneous electrocardiography (ECG) changes had occurred. PTCA was considered successful if residual stenosis, as determined by quantitative coronary angiography, was <30% and no major complications (myo-

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cardial infarction, bypass surgery, or death) had occurred. Angiographic measurements were performed off line, using a compact disk medical 3500 view station (Philips Medical Systems, Best, The Netherlands), by an experienced observer unaware of the scintigraphic findings. Measurements were obtained from a single projection that showed the most severe stenosis. The type of stent selected and the technique of implantation were left to the discretion of the operator. All patients were treated with ticlopidine for 1 mo and aspirin. Exclusion criteria were the presence of other lesions in the dilated vessel or of severe stenosis (>70% stenosis of the diameter by visual estimation) in the nondilated vessels, previous myocardial infarction, previous coronary bypass surgery, and local vascular complications precluding exercise within the week after PTCA. The Institutional Ethics Committee approved the study, and all patients gave written informed consent.

Exercise Test

The symptom-limited exercise test was performed within the week after PTCA (3–7 d). Twenty-one patients used a bicycle ergometer, and 9 used a standard treadmill. All antianginal drugs were withdrawn >24 h before the exercise test. When the bicycle ergometer was used, the test started with an initial load of 50 W, and 25 W were added every 3 min. When the exercise treadmill was used, the Bruce protocol was applied. Exercise testing was stopped if exhaustion, symptoms, or >2 mm ST-segment depression developed. Exercise testing was considered adequate if >80% of the maximal predicted heart rate or >5 metabolic equivalents of oxygen consumption were achieved without angina or ST-segment depression. Patients unable to exercise adequately received intravenous dipyridamole (0.14 mg/kg of body weight per minute for 4 min) while they continued to exercise at the maximal tolerated load up to 2 min after the end of dipyridamole administration. The exercise test result was considered positive if angina occurred or if ST-segment depression ≥ 1 mm appeared 0.08 s after the J point.

^{99m}Tc-Tetrofosmin SPECT

All patients received an intravenous dose of ^{99m}Tc-tetrofosmin (220 MBq) 30–60 s before the end of exercise. The stress and rest studies were performed 1–2 h apart, and the dose for the rest study was 650 MBq. Images were acquired 1 h after administration of the radiopharmaceutical using an SP4 scintillation camera (Elscint Ltd., Haifa, Israel) with a high-resolution collimator and a semicircular orbit starting at a 30° right anterior oblique position, with detection performed every 3°. Reconstruction was performed (Butterworth filter; order, 5; section frequency, 0.4), and short-axis, horizontal long-axis, and vertical long-axis sections were obtained. Twelve segments were evaluated: anterobasal, midanterior, anteroapical, septobasal, midseptal, septoapical, inferobasal, midinferior, inferoapical, laterobasal, midlateral, and lateroapical. Myocardial uptake was assessed by 2 experienced observers, who reached a consensus and were unaware of the dilated vessel and follow-up findings. SPECT findings were considered positive when a mild, moderate, or severe defect was present on stress images in at least 2 of the 3 axes or in 3 consecutive tomographic sections on the same axis, with normal uptake at rest.

Follow-Up

All patients were followed up clinically, and 23 (77%) angiographically, at a mean (±SD) of 8 ± 3 mo after angioplasty. Major cardiac events were defined as target vessel revascularization, myocardial infarction, or death. Angiographic restenosis was defined as a ≥50% stenosis of the luminal diameter, as seen at follow-up angiography.

Statistical Analysis

Categoric values are expressed as frequencies. Continuous variables are expressed as mean ± SD or median with superior and inferior range. Univariate analyses were performed using the Fischer exact test for categoric values and the Student *t* test or the nonparametric Mann–Whitney test for continuous variables. $P < 0.05$ was considered statistically significant.

RESULTS

The baseline clinical characteristics of the study population are listed in Table 1. The mean age was 60 y, and 19 patients (63%) underwent coronary angiography and PTCA because of unstable angina (10 patients had class I or II unstable angina, and 9 patients had class III). Myocardial ischemia before PTCA was evidenced by positive treadmill results in 12 patients (40%), positive myocardial scintigraphy results in 9 patients (30%), and spontaneous ECG changes in 9 patients (30%).

Angiographic Characteristics and PTCA Results

Most patients ($n = 21$; 70%) underwent PTCA of the left anterior descending artery. The results of PTCA are described in Table 2. Thirty-four stents were implanted (26 patients received 1 stent and 4 patients received 2 stents), with a median diameter of 3.0 mm (range, 2.5–4.0 mm) and a median length of 15 mm (range, 8–24 mm). The majority of stents implanted were tubular (MultiLink [10 stents]; Guidant/ACS, Santa Clara, CA; Jostent [2 stents]; JOMED International AB, Helsingborg, Sweden; NIR stent [2 stents]; Medinol Ltd., Tel Aviv, Israel; MiniCrown [1 stent]; Johnson & Johnson Interventional Systems, Warren, NJ; Bestent [1 stent]; Medtronic Instent, Minneapolis, MN), 7 stents had a sinusoidal ring design (AVE GFX stent; Arterial Vascular Engineering Inc., Santa Rosa, CA), 4 stents comprised zigzag modules mounted on a flexible spine (XT coronary stent; Bard Ireland Ltd., Galway, Ireland), 3 stents were a self-expanding wire mesh (Wallstent; Schneider AG, Bulach, Switzerland), and 4 stents had a coil design (Crossflex; Johnson & Johnson).

TABLE 1
Patient Demographics ($n = 30$)

Characteristic	Value
Age (y)	60 ± 10
Female	8 (27%)
Smoker	6 (20%)
Hypertension	14 (47%)
Diabetes mellitus	10 (33%)
Hypercholesterolemia	22 (73%)
Unstable angina	19 (63%)
Demonstration of ischemia	
Treadmill testing	12 (40%)
Myocardial scintigraphy	9 (30%)
Spontaneous ECG changes	9 (30%)

TABLE 2
Coronary Angiography and Angioplasty Data

Characteristic	Value
No. of dilated vessels	
LAD	21 (70%)
LCX	5 (17%)
RCA	4 (13%)
Reference diameter (mm)	
Before PTCA	2.93 ± 0.59
After PTCA	3.11 ± 0.48
Minimal luminal diameter (mm)	
Before PTCA	0.89 ± 0.36
After PTCA	2.85 ± 0.45
Stenosis (% diameter)	
Before PTCA	68.5 ± 12.6
After PTCA	9.3 ± 8.8

LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA = right coronary artery.

Before the intervention, the mean minimal luminal diameter at the culprit lesion was 0.89 ± 0.36 mm and the mean stenosis grade was 68.6% ± 12.6%. After stent implantation, the corresponding values were 2.82 ± 0.45 mm and 9.3% ± 8.8%, respectively ($P < 0.001$).

Myocardial SPECT Exercise Test

The results of the exercise test are shown in Table 3. Exercise testing was performed at a mean of 6 ± 1 d after PTCA. Three patients (10%) could not exercise adequately and received an intravenous dose of dipyridamole. The findings were positive for 4 patients (2 with ECG changes and 2 with ECG changes added to angina). No complications occurred.

Myocardial SPECT showed myocardial defects in the territory of the dilated artery in 5 patients (17%). The dilated artery was the left anterior descending artery in 2 patients, the left circumflex artery in another 2, and the right coronary artery in 1. The myocardial defect was evaluated as moderate in all but 1 patient, in whom it was mild. Only 1 of these 5 patients had significant ST depression during exercise. As shown in Table 4, no angiographic or procedural differences were seen between patients with and patients without early ischemic defects in the territory of the dilated artery.

TABLE 3
Exercise Test Results

Parameter	Value
Time after angioplasty (d)	6 ± 1
Metabolic equivalents of oxygen consumption	7 ± 1.9
Peak heart rate (bpm)	129 ± 25
% Predicted heart rate	79 ± 13
Peak systolic blood pressure (mm Hg)	180 ± 20
Peak rate–pressure product (bpm · mm Hg · 10)	23.5 ± 1.9
No. of patients taking dipyridamole	3 (10%)
No. of patients with ST depression ≥ 1 mm	4 (13%)
No. of patients with angina	2 (7%)

TABLE 4
Comparison of Patients With and Patients Without Myocardial Defects in Territory of Dilated Artery

Parameter	Myocardial defects: Present ($n = 5$)	Myocardial defects: Absent ($n = 25$)	P
No. of stents per patient	1.0	1.1	0.35
Stent length (mm)	17.0 ± 4.8	16.3 ± 3.4	0.72
Stent diameter (mm)	3.0 ± 0.35	3.09 ± 0.36	0.61
Maximum inflation pressure (atm)	11.8 ± 1.7	12.9 ± 1.5	0.15
Reference diameter before angioplasty (mm)	2.92 ± 0.54	2.92 ± 0.60	0.98
Stenosis (% diameter)	65.1 ± 15.9	69.2 ± 12.1	0.51
Minimal luminal diameter before angioplasty (mm)	1.02 ± 0.45	0.86 ± 0.34	0.38
Reference diameter after angioplasty (mm)	3.08 ± 0.47	3.11 ± 0.49	0.87
Residual stenosis (%)	12.5 ± 7.5	8.6 ± 9.1	0.38
Minimal luminal diameter after angioplasty (mm)	2.70 ± 0.52	2.84 ± 0.44	0.54

Another 5 patients had mild myocardial perfusion defects remote from the dilated artery. Two of these patients had presented with moderate coronary stenosis in the distal segment of a nondilated artery, and 3 had significant ECG changes during exercise (2 with added angina).

Follow-Up

Four patients (13%) underwent target lesion revascularization because of clinical restenosis (3 had recurrent angina, and 1 had a non–Q wave myocardial infarction). No deaths occurred before follow-up. Angiographic restenosis was detected by follow-up angiography in 6 (26%) of 23 patients.

Relationship Between Early Ischemic Defects in Territory of Dilated Artery and Restenosis

Angiographic restenosis occurred in 3 of 4 patients who had ischemic defects and underwent follow-up angiography (restenosis rate, 75%) and in 3 of 19 patients who had no ischemic defects and underwent follow-up angiography (restenosis rate, 16%) ($P = 0.04$). Two of the 5 patients with early myocardial defects underwent target lesion revascularization (40%), compared with only 2 of 25 patients without early ischemic defects (8%) ($P = 0.18$; Fig. 1). At the time of follow-up, none of the patients with significant ECG changes during exercise testing had experienced clinical events.

Maximal exercise (plus dipyridamole) ^{99m}Tc-tetrofosmin myocardial SPECT performed early after stent implantation had a specificity of 94%, a sensitivity of 50%, and positive and negative predictive values of 75% and 84%, respec-

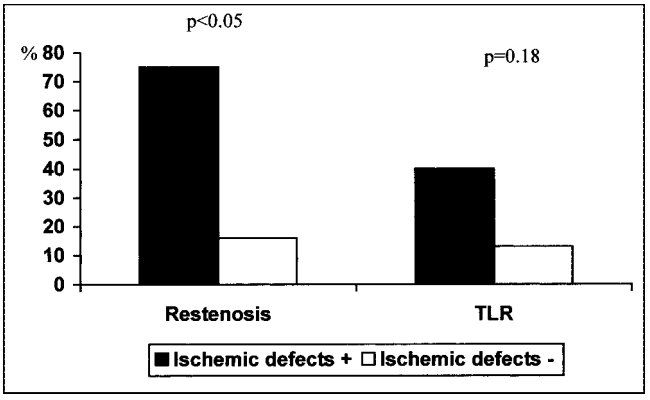

FIGURE 1. Relationship between maximal exercise (plus dipyridamole) myocardial SPECT results early after coronary stent implantation and occurrence of angiographic and clinical restenosis at follow-up. TLR = target lesion revascularization.

tively, for the prediction of restenosis. Regarding target lesion revascularization at follow-up, specificity, sensitivity, and positive and negative predictive values were 88%, 50%, and 40% and 92%, respectively.

DISCUSSION

Coronary angioplasty with stent implantation was associated with a 17% rate of myocardial defects early after the procedure, as assessed by maximal exercise (plus dipyridamole) ^{99m}Tc-tetrofosmin SPECT. Detection of these residual ischemic defects was associated with a high angiographic restenosis rate, although only half of the restenotic events occurred in patients with residual ischemia after stent implantation.

This study compares favorably with the 30%–50% incidence of myocardial perfusion abnormalities reported early after coronary balloon angioplasty, suggesting that some of the myocardial defects present early after balloon angioplasty were caused by inadequate luminal enlargement and that the greater luminal area achieved with stent implantation resulted in a better functional result after angioplasty. Also, stents prevent elastic recoil and spasm at the dilated site, mechanisms that can contribute to early ischemic defects after balloon angioplasty (*16,17*). Similar results have been reported for measurement of coronary flow reserve immediately after balloon angioplasty and stent implantation. Coronary flow reserve remained abnormal in nearly 60% of patients after balloon angioplasty, whereas only 19% of patients had an inadequate flow reserve after coronary stent implantation (*14*). Likewise, the coronary flow reserve determined by PET in 15 patients within the first 3 d after coronary stent implantation showed normalization of myocardial blood flow in all cases (*18*). However, other studies using coil stents have reported lower rates (13%–60%) of functional recovery after coronary angioplasty (*19,20*). In this study, differences in the rate of coil stent implantation between patients with and patients without early myocardial defects were not statistically significant (20% vs. 12%, respectively).

Despite the functional improvement obtained after coronary stent implantation, compared with that obtained after balloon angioplasty, a minority of patients still had functional abnormalities. These early defects may be related to impairment of the microvascular response, microvascular stunning because of particulate embolization, or unapparent angiographic obstruction at or adjacent to the stent. To determine the potential mechanisms of flow abnormalities immediately after stent implantation, Kern et al. (*21*) measured the coronary flow velocity reserve in the artery containing the stent and in an angiographically normal reference vessel and found that at least half of the functional abnormalities after stent implantation were caused by global microvascular disease. According to our results, only 16% of the studied patients had myocardial flow abnormalities that could be attributed to residual vessel obstruction or to regional microvascular stunning caused by distal embolization in the territory of the dilated artery. Intravascular sonography studies have shown that stent expansion is often inadequate despite a satisfactory angiographic appearance after stent implantation (*22,23*). Other mechanisms of unappreciated luminal obstruction after stent implantation are unapparent stent-edge dissections or new accumulations of focally extruded plaque in an adjacent vessel with no stent (*24*). A high correlation has been shown between intravascular sonographic assessment of stent expansion and functional evaluation of coronary blood flow, and no correlation has been shown between quantitative angiographic assessment of stent expansion and coronary blood flow measurements (*20*). Moreover, an inverse relationship between optimal stent expansion, as assessed by intravascular sonography, and the probability of restenosis has been reported, suggesting that suboptimal stent deployment has an important role in the restenotic process (*25,26*). Nevertheless, absence of early myocardial ischemia may not exclude the possibility of restenosis, because half of angiographic restenosis in our study occurred in patients without residual ischemic defects.

There has been some doubt as to the safety of performing a functional test within the first few days after coronary stent implantation. This doubt is based on previous case reports documenting stent thrombosis within hours after stress testing (*27,28*). No episodes of stent thrombosis or of local vascular complications were observed in our study. Furthermore, a large, randomized study has shown that functional testing early after implantation of a coronary stent is safe (*29*).

This study had some limitations. Intravascular sonography was not routinely used to guide stent deployment. Sonography would have detected stent underexpansion or focal obstructions adjacent to the stent explaining some of the early myocardial defects. Also, determination of fractional flow reserve by pressure sensor wires would have differentiated the potential role of residual obstructions after

stent implantation from the role of microvascular dysfunction, because the latter does not affect values obtained with pressure wires (*30*). Incomplete angiographic follow-up prevents accurate assessment of the restenosis rate. There may be some asymptomatic patients with angiographic restenosis; identifying these patients could change the restenosis rate and alter the final results. However, the angiographic restenosis rate and clinical events at follow-up were similar to those observed in other studies (*31*,*32*), and rates of angiography at follow-up were nearly equal in patients with and patients without early ischemic defects (80% and 76%, respectively). Finally, the most important limitation of the study was the small sample size, which significantly lessened the potential of the results, especially those concerning the clinical significance of the test. The small number of patients with residual ischemic defects prevented us from reaching definite conclusions about their prognostic value.

CONCLUSION

In most patients, coronary stent implantation results in complete normalization of myocardial perfusion, as evaluated by maximal exercise (plus dipyridamole) myocardial ^{99m}Tc-tetrofosmin SPECT. However, 17% of patients were found to have persistent myocardial defects despite successful stent implantation and good angiographic results. Furthermore, the study findings suggest that detection of these early ischemic defects is associated with a high restenosis rate and that normal myocardial perfusion results identify a group of patients with a low risk of restenosis at follow-up. However, the clinical value of these findings has to be confirmed by larger studies.

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