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Early Recovery of Coronary Flow Reserve After Stent Implantation as Assessed by Positron Emission Tomography

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OBJECTIVES The aim of this study was to quantitatively evaluate myocardial flow reserve in patients early after coronary stent implantation using positron emission tomography.

BACKGROUND Delayed restoration of coronary flow reserve after percutaneous transluminal coronary angioplasty (PTCA) has been observed using a variety of techniques. Altered distal vasoregulation as well as residual stenosis have been considered possible explanations for this phenomenon. Although the implantation of stents may influence some of these mechanisms, little data are available characterizing coronary flow reserve early after stent placement.

METHODS In 14 patients 1.6 ± 0.6 days after stenting, N-13-ammonia positron emission tomographic studies were performed at rest and during adenosine-induced vasodilation. Myocardial blood flow was quantified using a three-compartment model. Rest and stress flow data, as well as coronary flow reserve of stented vascular territories, were compared with that of remote areas.

RESULTS The stenosis decreased from 72.1 ± 7.3% to 3.7 ± 6.7% after stent implantation. Coronary flow in the stented areas did not differ significantly from that in remote areas either at rest (76.1 ± 18.5 and 75.7 ± 17.7 ml/min/100 g, respectively), or during maximal vasodilation (205.5 ± 59.9 and 179.4 ± 47.4 ml/min/100 g, respectively). In addition, there was no significant difference in the calculated values of coronary reserve of these two regions (2.74 ± 0.64 and 2.43 ± 0.55, respectively).

CONCLUSIONS The mechanical support of dilated arteries by a stent not only restores the macroscopic integrity of epicardial arteries, but also results, in contrast to conventional PTCA procedures, in early recovery of flow reserve. (J Am Coll Cardiol 1999;34:1036–41) © 1999 by the American College of Cardiology

The delayed restoration of coronary flow reserve is a well-known phenomenon in vascular territories that have undergone coronary angioplasty. Studies with ^{201}Tl perfusion scintigraphy (1), ^{15}O-water positron emission tomography (PET) (2), Doppler catheter flow measurement (2,3) and quantitative cine angiography (4,5) have demonstrated

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sustained abnormalities in coronary flow reserve during the first days after percutaneous transluminal coronary angioplasty (PTCA). Based on these studies, a further improvement of coronary flow reserve can be expected one week to three months after the intervention. The pathophysiology of these slow changes is still unclear. The effect of vasoactive agents released at the site of dilation due to the mechanical trauma of intervention has been considered as a possible etiology (6), as has a transient defect in distal resistance vessel autoregulation (2,3). Other studies have discussed the role of local spasm, or the dynamic recoil of the artery wall at the site of earlier stenosis (7,8), suggesting the dominant role of anatomical integrity of epicardial arteries at the site of previous stenosis.

The implantation of stents may influence some of these proposed mechanisms. The supplementary procedure of stent positioning may induce additional release of vasoactive agents. On the other hand, the metallic frame can prevent changes in artery diameter at the site of previous dilation.

Therefore, we hypothesized that the mechanical instability of the coronary artery wall after PTCA is the determining factor of slow recovery of distal coronary reserve after

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Abbrevations and Acronyms:

LAD	=	left anterior descending artery
LCX	=	left circumflex artery
PET	=	Positron emission tomography
PTCA	=	percutaneous transluminal coronary angioplasty
RCA	=	right coronary artery

intervention. The implantation of stents stabilizes the artery wall and ensures a coronary reserve comparable with that of nondilated arteries early after the revascularization procedure. To test this hypothesis, we quantified coronary blood flow at rest and during adenosine-induced maximal vasodilation and calculated the coronary reserve of stented and control vascular territories in patients one to three days after coronary stent implantation.

METHODS

Patient population. Dynamic N-13-ammonia PET was performed at rest and during maximal vasodilation in 14 patients after stent implantation. The 13 men and 1 woman underwent the revascularization procedure 1 to 3 days (average 1.6 ± 0.6 days) before the scintigraphic investigation. Exclusion criteria consisted of patients with previous myocardial infarction, myocardial hypertrophy or triple-vessel disease. The mean age of the patients was 59.1 ± 8.4 years (range 39 to 72 years). In four cases, the indication for stent implantation was dissection or threatening dissection, and in 10 cases, unsatisfactory results after balloon dilation.

Coronary angiography and interventional procedure. Selective right and left coronary angiography was performed according to the Judkins method with a digital angiography system; images were stored digitally (Hicor; Siemens, Erlangen, Germany). The angiograms were analyzed off-line on a digital angiographic workstation (AWOS; Siemens). For quantitative analysis of luminal diameter at the culprit lesion, the projection was chosen that showed the highest grade of stenosis. The details of this automated computer-based analysis system have been previously described (9). Percent diameter stenosis was calculated using minimal diameter and interpolated reference diameter.

PTCA and placement of Palmaz-Schatz stents (Johnson & Johnson Interventional Systems, Warren, NJ) were performed via femoral approach using 7 French sheaths. The Stents were hand-crimped onto the angioplasty balloon and deployed as previously described in detail (10). To improve stent expansion, additional balloon inflations were performed at high pressure (>15 atm) using a 10-mm balloon (High Energy; Boston Scientific, Natwick, Massachusetts).

PET. Nitrogen-13 ammonia was produced by ^{16}0 (p,alpha) ^{13}N reaction as described previously (11). Patients were instructed to discontinue cardiac medications the evening before the PET study. Each subject was positioned in the Siemens ECAT 951R/31 whole body scanner, which has 16 circular detector rings yielding 31 reconstructed transaxial planes (slice separation 3.4 mm). A 15-min transmission scan was acquired and used to determine attenuation correction factors.

After the transmission data acquisition, 20 mCi of N-13 ammonia was injected intravenously and a 20-min, 21-frame dynamic PET acquisition was initiated (12 × 10 s, 6 × 30 s, 3 × 300 s). An additional period of 30 min was allowed for the decay of N-13 ammonia, at which time adenosine (0.14 mg/kg/min) was infused intravenously for 5 min. After 2 min, a second injection of 20 mCi of N-13 ammonia was administered. The dynamic PET acquisition was then repeated.

The transaxial data were reconstructed by using a Hanning filter with a cutoff frequency of 0.4 cycles/pixel. The reconstructed images were reoriented along the long axis of the heart to yield images in the short-axis plane of the left ventricle by using a SUN workstation (SUN Microsystems Inc., Palo Alto, California) and commercial imaging analysis software (CTI, Knoxville, Tennessee).

Based on the short-axis planes, myocardial time-activity curves were generated by an automated sampling routine previously developed and validated (12). According to the described algorithm, 12 myocardial sectors were defined in each of six planes encompassing nearly the entire left ventricle. The regions were defined by the image planes of the last time frame of the dynamic study sequence and then copied to all other time frames of the dynamic sequence. Before time-activity curves were generated, the dynamic image set was corrected for patient motion with a semi-automated program. The dynamic image set was sampled and 72 (six planes × 12 sectors) time-activity curves were stored. From this data set, the average time-activity curve of the basal and distal portions of the anterior, lateral, inferior walls, as well as the septum were generated and used for further analysis.

The input activity was derived from the central ventricular area of the basal midventricular planes. A three-compartment model described by Hutchins et al. (13) was fitted to the averaged time-activity data. The K1 variable of the model provides a direct estimate of myocardial blood flow. The model also corrects for partial volume effect and spillover of activity from blood pool to myocardium using a variable for the total blood volume in the region of interest (13). Baseline K1 and adenosine K1 values were determined as measures of rest and maximal blood flow, respectively. The ratio of maximal flow to rest flow was calculated as myocardial flow reserve.

To match coronary artery anatomy to myocardial regions analyzed by this program, data from basal-anterior, distal-anterior, basal-septal and distal-septal regions were assigned to the left anterior descending artery (LAD), data from basal-lateral and distal-lateral regions to the left circumflex artery (LCX), while basal-inferior and distal inferior regions to the right coronary artery (RCA). Additionally, data from

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Table 1. Clinical and Coronary Angiographic Data in 14 Patients

Patient	Age (yrs)	Stented Artery	Reference Artery	Artery Not Involved in the Evaluation	Before Stenting		After Stenting	
					MLD	Stenosis (%)	MLD	Stenosis (%)
1	39	LAD	LCX	RCA	0.9	73	2.7	18
2	59	RCA	LAD, LCX	no	0.6	74	3.2	−3
3	66	RCA	LAD	LCX	0.4	86	3.2	−10
4	56	LAD	LCX	RCA	0.7	79	3.2	11
5	50	LAD	RCA	LCX	0.5	83	3.0	3
6	70	LAD	LCX	RCA	1.2	65	3.2	6
7	49	RCA	LAD, LCX	no	0.7	77	3.3	−3
8	72	RCA	LAD	LCX	1.2	63	3.8	12
9	50	LAD	RCA	LCX	1.3	59	3.0	3
10	72	LCX	LAD, RCA	no	0.5	83	3.1	−3
11	67	LAD	RCA, LCX	no	1.0	64	3.2	9
12	56	RCA	LCX	LAD	1.1	62	3.5	0
13	66	LAD	RCA, LCX	no	1.0	68	3.1	3
14	55	LAD	LCX	LAD	0.8	73	3.0	6
Mean	59.1				0.85	72.1	3.18	3.7
SD	8.4				0.25	7.3	0.17	6.7
p values versus before stenting							< 0.0001	< 0.0001

LAD = left anterior descending artery; LCX = left circumflex artery; MLD = minimal luminal diameter; RCA = right coronary artery.

vascular territories of stented arteries were compared with those of reference arteries (remote areas). A coronary artery was considered suitable to be used as reference if it did not have a discrete stenosis (>30%). If two such vascular territories were present in a patient, the averaged myocardial blood flow of these territories was used in the calculation.

Statistical analysis. Values were reported as mean ± standard deviation. Data from stented and remote areas, as well as the hemodynamic parameters at baseline and during vasodilation, were analyzed with the paired Student *t* test. A p value of < 0.05 was considered statistically significant.

RESULTS

Coronary angiography. The culprit lesions treated by stent implantation were located in the RCA in five cases, in the LAD in eight cases and in the LCX in one case. Based on

Table 2. Myocardial Blood Flow (ml/min/100 g) and Coronary Flow Reserve by Positron Emission Tomography

Patient	Remote Area			Stented Area		
	Rest Flow	Adenosine Flow	CR	Rest Flow	Adenosine Flow	CR
1	62	199	3.2	68	226	3.3
2	64	212	3.3	64	208	3.2
3	78	196	2.5	96	218	2.3
4	65	200	3.1	66	187	2.8
5	65	204	3.1	63	283	4.5
6	89	151	1.7	88	343	3.9
7	95	209	2.2	96	156	1.6
8	87	142	1.6	79	160	2.0
9	43	100	2.3	54	150	2.8
10	155	368	2.4	134	374	2.8
11	86	149	1.7	85	203	2.4
12	43	137	3.2	50	153	3.1
13	54	88	1.6	52	85	1.6
14	79	157	2.0	65	131	2.0
Mean	76.1	179.4	2.43	75.7	205.5	2.74
SD	18.5	47.4	0.55	17.7	59.9	0.64
p values versus remote				0.89	0.119	0.1292

CR = coronary reserve.

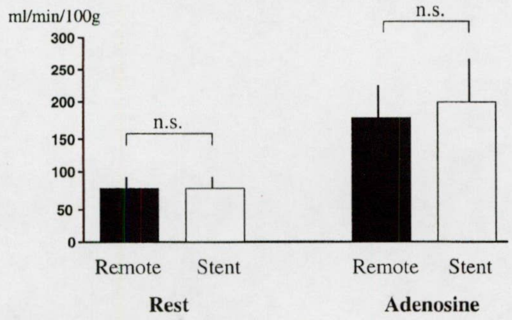

Figure 1. Coronary flow at rest and during adenosine-induced vasodilation in remote and stented vascular territories in 14 patients.

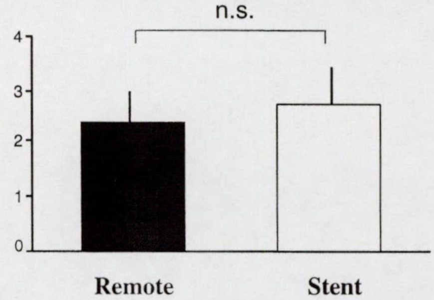

Figure 2. Coronary flow reserve in remote and stented vascular territories.

the criteria of ≥50% stenosis, only one of the 14 patients had a significant stenosis in a nonstented artery. In eight cases, however, minor stenoses (<50%) were present in one of the nonstented arteries. As reference territory, only the 19 arteries without minor stenoses were considered. All patients had at least one such vascular territory (Table 1).

Before the intervention, the mean minimal luminal diameter at the culprit lesion was 0.85 ± 0.25 mm and the stenosis grade was 72.1 ± 7.3%. After the implantation of stents, the corresponding values were 3.18 ± 0.17 mm and 3.7 ± 6.7%, respectively.

Adenosine response. The systolic blood pressure did not change significantly between the start of adenosine infusion and the time of N-13-ammonia injection (128.9 ± 14.1 vs. 128.9 ± 15.9 mm Hg). However, diastolic blood pressure decreased (76.8 ± 6.3 vs. 70.7 ± 6.6 mm Hg, $p = 0.018$), while the heart rate increased significantly during this period (64.1 ± 10.4 vs. 80.8 ± 7.8, $p = 0.001$).

Myocardial blood flow and flow reserve. The mean myocardial blood flow at rest in the reference region was 76.1 ± 18.5 ml/min/100 g and increased to 179.4 ± 47.4 ml/min/100 g during maximal vasodilation (Table 2). The myocardial blood flow did not differ significantly in the territories supplied by stented arteries, neither at rest or during vasodilation, with values of 75.7 ± 17.7 ml/min/100 g ($p = 0.89$) and 205.5 ± 59.9 ml/min/100 g ($p = 0.119$), respectively (Fig. 1).

The coronary flow reserve was 2.43 ± 0.55 in the reference region and 2.74 ± 0.64 in the areas supplied by stented arteries ($p = 0.129$) (Fig. 2).

DISCUSSION

The results of our study demonstrate that myocardial blood flow at rest and during maximal vasodilation is similar in the territory of stented arteries as compared with remote areas within the first 3 days after stent implantation.

Flow changes after PTCA. Several studies performed in the first few days after PTCA have demonstrated a relative decrease in coronary flow reserve in comparison with remote areas (2–4,14–16). The cause of this slow recovery is, however, unclear. The possible role of flow-limiting residual stenosis after the intervention was demonstrated only by Zijstra et al. (5). Most of the authors considered factors involving the distal vasoregulation, resulting in an increase of resting flow (2,14,15), or restricting stress flow (2,14).

Flow changes after stent implantation. Studies defining flow changes after stent implantation are rare, but recent results using quantitative angiography and Doppler flow wire techniques have been published (17,18). According to these studies, the moderate improvement in coronary reserve after balloon dilation and its normalization after stent implantation correlate well with changes in minimal luminal diameter during the procedures. These authors did not find a significant change in resting blood flow, so the alteration of coronary flow reserve was the consequence of improved myocardial flow at maximal vasodilation (17). According to their data, the stress flow reached a similar level in the stented vascular territory as in remote areas. These reported data are in agreement with the present results.

Angiographic result of PTCA. In most clinical centers, PTCA is considered successful if the residual stenosis is <50%. Consequently, the average residual stenosis in the studies mentioned above ranged between 18% and 37%. Additionally, the minimal luminal diameter is a dynamically changing index after this intervention. The treated segments are prone to spasm and elastic recoil of the vessel wall. The increased susceptibility of dilated segments to coronary spasm was demonstrated by several studies after PTCA (7,19,20). According to El-Tamimi et al. (20), an average of 30% decrease in minimal luminal diameter can be demonstrated 4 h after PTCA, which is reversible after the administration of intracoronary nitroglycerin. This study also showed that the basal tone of dilated segments decreases with time, as assessed by repeated investigation at eight days. The time course of basal coronary tone change is similar to that of coronary flow impairment reported after PTCA (1–5). A second recently discussed factor altering the luminal diameter is the remodeling of coronary arteries. Studies suggest the importance of this mechanism in the

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development of restenosis after PTCA (21–23). Recently, De Franco and Topol suggested its pathophysiological role also in the late restoration of coronary reserve (24).

Macroscopic result after the stent implantation. In contrast to PTCA, the implantation of stents in most cases normalizes the contour of treated vessels. The difference in angiographic results between PTCA and stent implantation has been shown in several studies (9,25–27). Accordingly, the value of residual stenosis in our stented population was only 3.5 ± 8%. Furthermore, the luminal diameter is expected to be stable after this intervention. Serial intravascular ultrasound studies have failed to show evidence of chronic stent recoil early after intervention (28,29). The restoration of coronary flow reserve in our patient population, where residual stenoses were practically absent, supports the theory that the minimal luminal diameter is determinant regarding distal coronary reserve.

However, stress flow and coronary reserve tended toward higher values in the stented vascular territories compared with the control areas. This interesting observation may reflect chronic vascular adaptation in the poststenotic vascular bed. The long-standing reduction of perfusion pressure in these areas may induce an increased perfusion capacity, but not an altered relationship between slow and normal perfusion pressure, as it was suggested earlier by several authors (2,14,15). The normal resting blood flow, rather, supports the notion of an intact vasoregulation in these areas. The presumed enhanced peripheral vasodilatory capacity of poststenotic areas may have been masked by local restriction of epicardial vessel segments after PTCA in earlier studies.

Study limitations. In this study, myocardial blood flow was quantified in stented vascular territories and the data were compared with the results from remote areas in the same patients. A direct comparison with a healthy population using the same technique was not performed. Previous studies have demonstrated that patients with proven coronary artery disease have abnormal coronary flow reserve in angiographically normal arteries (30,31), as do patients without angiographic evidence for coronary heart disease, but with risk factors for coronary artery disease (32). Therefore, the comparison of various vascular territories within a given patient appeared to be more appropriate than relating the results to a healthy control population.

The patients were only evaluated early after intervention and no late follow-up was performed. However, the preliminary analysis of the first six patients suggested full restoration of coronary flow reserve at the time of early investigation. Due to the follow-up results of three patients (1 to 3 days and 2 weeks after intervention), where similar coronary flow reserve values were found, (rest flows were 70.8 and 65.7 ml/min/100 g, stress flows were 244.7 and 226.3, while coronary reserves were 3.5 and 3.5, respectively, in control and stented territories), the subsequent follow-up studies were discontinued to reduce the logistic complexity of the study and to minimize radiation exposure to the patients.

An additional limitation of our study is that it did not include flow measurement data before the intervention. This was due to the logistics of stent implantation. The decision to implant stents was made only during the revascularization procedure; therefore, prior PET measurements could not be performed selectively. However, based on the coronary angiographic data of our population and the results of previous studies demonstrating the close correlation between coronary stenosis severity and distal coronary flow reserve (33,34), it is reasonable to assume a significantly reduced flow reserve before the interventions.

Clinical implications. Early restoration of coronary flow reserve after revascularization is important in acute and chronic ischemic syndromes in order to minimize the sequalae of regional induced ischemia. It also provides further support for early mobilization and return to daily activities. Although no direct comparison with PTCA was performed, the data confirm the notion that stent placement results in a complete and stable restoration of anatomy and function early after intervention. The delayed restoration of coronary flow reserve has limited the use of stress tests in the first weeks after PTCA, at a time when noninvasive tests are crucial to detect early restenosis. Based on our data, methods visualizing the heterogeneity of myocardial blood flow or blood flow reserve may be useful for the evaluation of stent patency early after its implantation. The clinical efficacy of such approaches requires prospective validation in the clinical setting of patients in whom restenosis is suspected.

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Myocardial Perfusion Scintigraphy to Evaluate Patients After Coronary Stent Implantation

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Coronary stent implantation is an increasingly accepted revascularization method. The 20%–30% restenosis rate during the first 6 mo requires a close follow-up of the patients. Since there is very little data available defining the role of perfusion scintigraphy in the management of this population, the aim of this study was to assess the diagnostic performance of stress myocardial perfusion imaging for detecting restenosis in patients after coronary stent implantation. **Methods:** In 82 patients, 93 rest or stress SPECT studies were performed using ^{201}Tl and ^{99m}Tc-hexakis-2-methoxyisobutyl isonitrile to evaluate 99 vascular territories with implanted coronary stents. The average interval between the stent implantation and the scintigraphic study was 210.5 ± 129.6 days. The scintiscans were visually evaluated. A stress-induced perfusion defect with reversibility at rest was used as the criterion for stent restenosis. **Results:** Coronary angiography revealed a stenosis of > 50% diameter in the region of the stent in 19 arteries, while in 80 arteries there was no evidence of restenosis angiographically. With perfusion scintigraphy, 15/19 vascular territories with restenosed stents showed stress-induced perfusion abnormalities (sensitivity = 79%), while 62/80 territories without restenosis did not (specificity = 78%). In territories without a myocardial infarction (n = 48), sensitivity and specificity values were 8/8 (100%) and 36/44 (82%), and in territories with a myocardial infarction (n = 47) 7/11 (64%) and 26/36 (72%), respectively. Side branch stenosis was fairly frequent in patients without stent restenosis but with a reversible perfusion pattern on their scintiscan (8/18); however, these stenoses were induced infrequently by the stents (3 cases). **Conclusion:** Using the criterion of defect reversibility, stress perfusion SPECT can accurately detect restenoses of coronary artery stents. This method is most accurate for evaluating patients without a previous myocardial infarction in the stented vascular territory.

Key Words: radionuclide imaging; SPECT; exercise tests; stent implantation

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Among the newly developed myocardial revascularization techniques, the implantation of coronary stents has rapidly gained widespread clinical acceptance due to its proven reduced rate of late restenosis (*1–3*). Because of favorable initial stenting results, stents are presently implanted in patients with a complex coronary anatomy who have not undergone prior revascularization, such as patients with acute or chronic occlusions of the coronary arteries (*4,5*).

Regional perfusion reserve may be affected in some of these patients due to the obstruction of side branch arteries by the stent. The reported frequency of side branch stenoses at the time of implantation of the stents varies from 5% to 27% (*6–8*). The available data are uneven regarding the eventual functional significance of side branch stenoses (*6,8*).

Due to a restenoses rate for the implanted stent as high as 20%–30% during the first 6 mo (*9–12*), these patients require close clinical follow-up. The role of perfusion scintigraphy in the management of patients after other revascularization procedures has been defined by several studies (*13–17*); however, there are few data available assessing the effectiveness of this method in patients with a coronary stent implant. This study was designed to evaluate the accuracy of stress-myocardial perfusion SPECT for detecting restenosis of coronary artery stents in a population of patients with relatively complex abnormalities of the coronary arteries.

MATERIALS AND METHODS

Patients

Between January 1993 and August 1995 at the Technische Universität (Munich, Germany) in 82 patients with coronary stents, 93 perfusion scintigraphic studies were performed during the chronic phase after intervention (more than 31 days after stent placement). Coronary angiography was available within 31 days of the scintigraphic studies in all cases. Perfusion scintigraphy and 6-mo coronary angiography were parts of a prospective routine follow-up of patients in most of the cases (60 cases). The additional investigations were performed based on clinical suspicion for restenosis (14 cases) or remote stenosis (19 cases). In 11 patients, two stress perfusion studies and two coronary angiographies were performed due to clinical indications. There were no data suggesting changes of clinical status during the time interval between scintigraphy and angiographic evaluation. All of the coronary angiographic investigations were matched with the corresponding perfusion scintigraphic result. Because in 6 patients coronary stent implants were present in 2 vascular territories, 99 stented vascular territories were included in the evaluation. The characteristics of the patient population are summarized in Table 1.

The coronary stent placements were done at 210.5 ± 129.6 days (35–875 days) before the scintigraphic studies. The mean time interval between scintigraphic and coronary angiographic investigations was 0.9 ± 9.8 days (range −31–31 days).

In 34 cases, the stents were positioned in the right coronary artery (RCA); in 50 cases in the left anterior descending artery (LAD); in 10 cases in the left circumflexus artery (LCX); and in 5 cases in a saphenous venous aorto-coronary graft. Previous myocardial infarctions in the stented vascular territory were present in 47 cases documented by the clinical history of the patients or by their electrocardiograms (ECGs). Data regarding any previous posterior wall myocardial infarction was matched to the RCA or LCX based on the results of coronary angiography and ventriculography.

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TABLE 1
Characteristics of Patient Population at First Investigation

Characteristic	Number
Age (average ± s.d. yr)	59.9 ± 10.2
Gender (male/female)	61/21
Vessels with ≥ 50% stenosis	
0	21
1	32
2	21
3	8
Previous	
Coronary bypass operation	10
Number of bypass grafts	26
Myocardial infarction	48

Number of patients = 82.

TABLE 2
Characteristics of Exercise Performance

Characteristic	Baseline	Maximum
Heart rate (bpm)	70.8 ± 14.7	140.1 ± 20.4
RR systolic (mm Hg)	134.1 ± 19.2	18.4 ± 25.4
RR diastolic (mm Hg)	79.9 ± 10.7	94.3 ± 12.1

Number of exercise studies = 83; Double product (mm Hg/min 100) = 257.4 ± 62.0; 85% of age predicted maximal heart rate not achieved = 22.

Stress Testing

Eighty-three studies were performed after treadmill exercise using a standard Bruce protocol to a symptom-limited endpoint or to > 85% age-predicted maximal heart rate of the patients. The radiotracer was injected intravenously at peak exercise, and the patients were asked to continue exercise for 1–2 additional min.

In 10 patients who were unable to exercise, dipyridamole stress tests were performed with a 4-min infusion of 0.14 mg/kg/min dipyridamole (*18*). The radiotracer was administered 4 min after the end of the dipyridamole infusion.

Clinical symptoms, for example the appearance of dyspnea or angina, were documented during the stress tests. A horizontal or downsloping ST-depression ≥ 1 mm in standard leads and ≥ 2 mm in precordial leads was considered a significant change indicating the presence of myocardial ischemia.

Scintigraphy

In 28 patients, studied before June 1994, ^{201}Tl stress-reinjection imaging protocol was used (*19,20*). The stress acquisitions were started within 15 min of stress injection of 3 mCi ^{201}Tl using a Siemens MultiSPECT (Knoxville, TN) triple-head or Siemens Diacam single-head camera equipped with high-resolution, low-energy collimators. Three hours after the stress injection of the tracer, an additional 1 mCi dose of ^{201}Tl was injected at rest and the acquisition was repeated 30 min later.

After June 1994, 65 studies were performed using the rest ^{201}Tl/stress ^{99m}Tc-MIBI protocol proposed by Berman et al. (*21*). The doses of ^{201}Tl and ^{99m}Tc-MIBI were 3 and 25 mCi, respectively. The acquisitions were started at least 30 min after injections of the tracers.

The images were acquired for 40 sec in 32 steps between the right anterior 45° and left posterior 45° positions, then stored in 64 × 64 matrix. For all cases, a Butterworth filter was used for filtered backprojection with a cutoff frequency of 0.45, order 5. The reconstructed transaxial slices were reoriented according to the long axis of the heart. Paired images of stress and rest short-axis and vertical and horizontal long-axis slices were generated for visual analysis. The tracer distributions in the vascular territory of stented arteries were classified in individual cases as: (a) normal; (b) stress-induced perfusion defect with complete normalization at rest (reversible defect); (c) stress-induced perfusion defect with incomplete normalization at rest (partially reversible defect); and (d) perfusion defect at stress without significant improvement at rest (persistent defect) by the consensus of three experienced readers. The observers had knowledge of the results of coronary angiography at the time of stent implantation but were unaware of the results of the control coronary angiography. The assignment of myocardial segments to individual vessels was guided by the coronary anatomy obtained from angiograms recorded at the time of stent implantation. Either a reversible defect or a partially reversible defect was considered a sign of stent restenosis.

Coronary Arteriography

Selective right and left coronary angiography and the visualization of bypass grafts, if present, were performed according to the Judkins method. To determine the luminal diameter at the location of stent and the adjacent reference regions, the projection was chosen that showed the highest grade of stenosis. Due to inability to visualize the Palmaz-Schatz stent clearly by radiographs, no attempts were made to distinguish whether restenosis lay within or in the proximal or distal segments adjacent to the stent. The percent diameter of the stenosis was graded as wall surface irregularity, ≥ 25%, ≥ 50%, ≥ 75%, ≥ 90%, ≥ 99% stenosis or total occlusion. Restenosis was defined as a diameter of stenosis ≥ 50%.

Statistical Analysis

Values were reported as mean ± s.d. Comparisons of proportions were performed by the chi-square test. A p value of < 0.05 was considered statistically significant. The sensitivity and specificity values were calculated as follows: sensitivity (%) = 100 × (true positives)/(true positives + false-negatives); specificity (%) = 100 × (true negatives)/(true negatives + false-positives).

RESULTS

Coronary Arteriography

Nineteen of 99 investigated arteries showed ≥ 50% stenosis at the site of the coronary stent at coronary angiography. The restenosed stents were located in the RCA (*5*), LAD (*10*), LCX (*3*) and in a coronary bypass graft to the LCX (*1*). Eleven stent restenoses were observed in the 47 stented regions with a previous myocardial infarction. There was no significant correlation between stent restenosis and a documented previous myocardial infarction.

Stress Perfusion Imaging

The characteristics of exercise performance and the results of perfusion scintigraphic studies are summarized in Tables 2 and 3. A persistent or only partially reversible perfusion defect was present in 35 of 47 (74%) vascular territories with a previous myocardial infarction, while 47 of 52 (90%) territories without myocardial infarction showed no defect at rest.

The sensitivity, specificity and accuracy indices of the clinical parameters of the stress tests, as well as that of the perfusion scintigraphic studies, are listed in Table 4. The transient perfusion pattern observed through scintigraphy identified 15/19 territories with stent restenosis (sensitivity 79%), while 62/80 territories without stent restenosis showed either the distribution of the tracer as normal or a perfusion defect without redistribution (specificity 78%). In the subpopulation of patients with previous myocardial infarction, stent restenosis was detected with a sensitivity of 7/11 (64%) and specificity of 26/36 (72%). In patients without a previous myocardial infarc-

TABLE 3
Scintigraphic Pattern of Stented Vascular Territories

Scintigraphic pattern	Whole population	Territories with AMI	Territories without AMI
Number	99	47	52
Normal	44 (44%)	9 (19%)	35 (67%)
Reversible defect	15 (15%)	3 (6%)	12 (23%)
Partially reversible defect	18 (18%)	14 (30%)	4 (8%)
Persistent defect	22 (22%)	21 (45%)	1 (2%)

AMI = acute myocardial infarction.

tion, sensitivity and specificity values were 8/8 (100%) and 36/44 (82%), respectively. The accuracy of the scintigraphic parameters was higher than that of the appearance of angina or a significant ECG abnormality during the stress tests (Table 4).

To evaluate the effectiveness of perfusion scintigraphy in a population less affected by referral bias, we separately analyzed the data of 65 territories in 60 patients who underwent perfusion scintigraphy prospectively as part of a 6-mo follow-up. The observed 80% sensitivity and 80% specificity values did not differ significantly from that of the whole population.

The effect of side branch stenoses on the scintigraphic findings was analyzed based on the 18 cases without stent restenosis but with a transient perfusion pattern on scintigraphy. Stenoses of the side branch arteries were detected in 8 of these 18 cases including the first diagonal artery of the LAD in 6 cases, the septal branch of the LAD in 1 case and the ramus posterolateralis of the RCX in 1 case. The development of side branch stenosis was documented angiographically at the time of the stent implantation in 3 cases (2 first diagonal and 1 septal branch stenoses), while in 5 other cases it existed before stent implantation. A perfusion abnormality on scintigraphy was typical for the first diagonal stenosis including only the basal anterolateral area of the left ventricle in 2 of 8 cases. The association of a small, reversible perfusion abnormality, located at the basal area of the anterior septum, was also clear as to severe stenosis of the septal branch of the LAD (Fig. 1). In 4 cases with first diagonalis stenosis, we were, however, not able to distinguish the induced perfusion abnormality from the expected vascular territory of the stented LAD. Similarly, in the patient with stenosed ramus posterolateralis, the induced perfusion defect did not differ significantly from the expected vascular territory of the ramus circumflexus.

In addition to the 8 cases with side branch stenosis, there was a discrepancy between the coronary angiographic findings regarding stent restenosis and the presence or absence of defect reversibility on scintigraphy in 14 cases. In 4 of these 14 cases, a stenosis was detected in other regions of the stented arteries, which were responsible for the transient pattern on scintigraphy in the absence of restenosis of the stent. In 6 cases, the coronary angiographic findings did not give a reasonable explanation for the transient perfusion abnormality on scintigraphy. In 4 cases, the reason for the discrepancy was the lack of defect reversibility in the presence of stent restenosis. All of these cases were in vascular territories with a previous myocardial infarction. The severity of the luminal stenosis in the area of the stent was 50% in 2 cases and 75% in the other 2 cases.

DISCUSSION

The results of this study show that stress myocardial perfusion imaging using the criterion of defect reversibility has a good diagnostic performance for detecting restenosis in patients after coronary stent implantation. Sensitivity and specificity values are higher in territories without a previous myocardial infarction.

Using the defect reversiblity criterion, we identified 79% of vascular territories with and 78% without restenosis in the region of the implanted coronary stents. These values are comparable to those reported for SPECT in the primary detection of coronary artery disease in individual native arteries (sensitivity 73% and 79%, specificity 83% and 84%, respectively) (*22,23*). For the identification of restenosis in individual arteries after percutaneous transluminal coronary angioplasty (PTCA), the reported sensitivity values are ranging between 75% and 94%, while the specificity is ranging between 84% and 93% (*14–17*). Most of these data are, however, based on a selected population of patients with a low prevalence of either multivessel disease or a previous myocardial infarction (*15–17*).

The effect of a previous myocardial infarction on the accu-

TABLE 4
Sensitivity, Specificity and Accuracy Values of Stress Tests and Perfusion Scintigraphy for Evaluation of Stent Restenosis in Different Patient Subpopulations

	All territories	Territories with AMI	Territories without AMI
Number	99	47	52
Angina at stress test			
Number	16	7	9
Sensitivity (%)	5/19 (26%)	1/11 (9%)	4/8 (50%)
Specificity (%)	69/80 (86%)	30/36 (83%)	39/44 (89%)
Accuracy (%)	74/99 (75%)	31/47 (66%)	43/52 (83%)
Significant ECG change during stress test			
Number	30	17	13
Sensitivity (%)	4/19 (21%)	2/11 (18%)	2/8 (25%)
Specificity (%)	54/80 (68%)	21/36 (58%)	33/44 (75%)
Accuracy (%)	58/99 (59%)	23/47 (49%)	35/52 (67%)
Transient perfusion on scintigram			
Number	29	15	14
Sensitivity (%)	15/19 (79%)	7/11 (64%)	8/8 (100%)
Specificity (%)	62/80 (78%)	26/36 (72%)	36/44 (82%)
Accuracy (%)	77/99 (79%)	33/47 (70%)	44/52 (85%)

ECG = electrocardiogram; AMI = acute myocardial infarction.

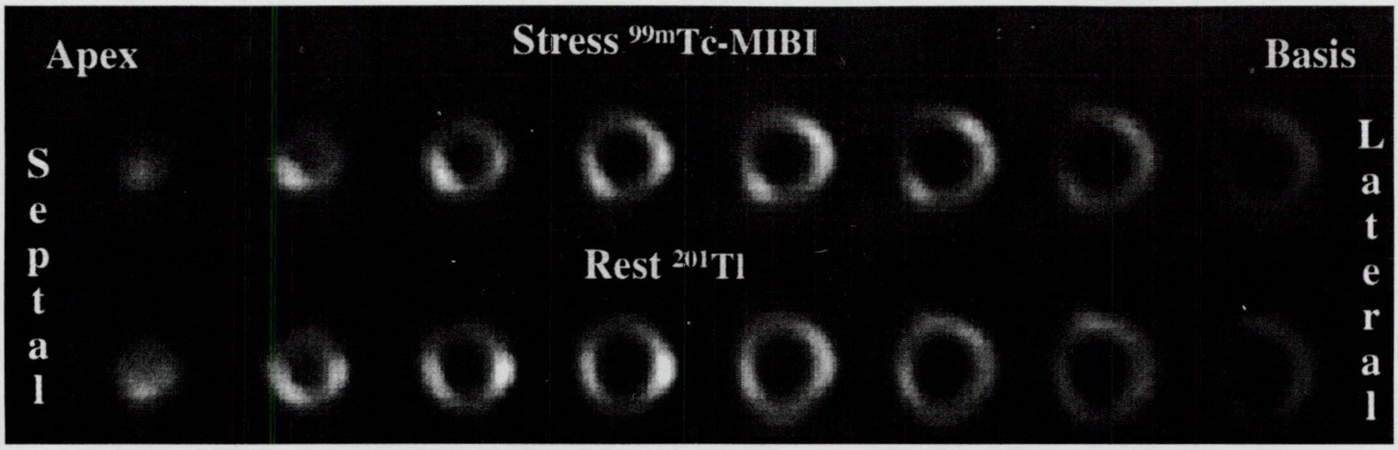

FIGURE 1. Short-axis SPECT images of patient with sequential coronary stents in proximal portion of LAD. At time of stent implantation, significant stenosis developed at origin of septal branch artery in this patient. Technetium-99m-MIBI stress images show small area with hypoperfusion in basal, anteroseptal region. Thallium-201 rest images demonstrate normal tracer distribution. Coronary angiography demonstrated no significant restenosis in region of implanted stents. Reversible perfusion abnormality on stress scintigraphy corresponds to stenosis of side branch artery.

racy of the test results was documented in our study by comparing the subgroups with and without previous myocardial infarctions. We found the sensitivity and specificity values for detecting stent restenosis very high in territories without a previous myocardial infarction (100% and 82%, respectively) and relatively lower in territories with a previous myocardial infarction (64% and 72%, respectively).

The evaluation criteria in most of the earlier studies was the detection of any coronary stenosis in a vascular tree (*22,24*). Using this method, the inclusion of territories with a myocardial infarction, which may be detected more reliably due to severe perfusion abnormalities, increased the overall effectiveness of the test. The clinical question in patients with regional revascularization is, however, the detailed analysis of regional myocardial perfusion distribution rather than the global evaluation of the three main vascular territories. Our study population also consisted of territories with a previous myocardial infarction in which the coronary stent was implanted to treat a residual stenosis. The scintigraphic evaluation of stent restenosis in such cases is limited due to pre-existing perfusion abnormalities. The reduced accuracy of perfusion scintigraphy was reported in a previous study analyzing vascular territories with a previous myocardial infarction and subsequent revascularization procedure (*13*). The sensitivity and specificity using the planar imaging method were only 50% and 79%, respectively (*13*).

Reversible perfusion defects appeared, however, also without stent restenosis. We found 18 such cases in our population. The most frequent anatomical abnormality observed, inducing reversible defect without stent restenosis, was stensois of the side branch arteries (8 cases). The development of side branch stenoses is a known complication of stent implantation. Its reported frequency at the time of implantation varies from 5% to 27% (*24–26*). The available data are uneven regarding the eventual evolution of side branch stenoses (*24,26*). In our population, 3 of the 8 side branch stenosed cases were revealed in patients enrolled prospectively in the study and 2 were revealed on scintigraphy that evaluated the hemodynamic significance of known stenoses in other vascular territories. In 3 cases, perfusion studies were clinically indicated by patient complaints. The development of ostial stenosis in the side branches at the time of stent implantation was documented in 3 of the 8 cases (2 at the origin of the first diagonal and 1 at the origin of the septal branch of the LAD). Two of these patients were enrolled in our study because of chest pain. The scintiscans of these patients revealed, however, only small perfusion abnormalities located in the basal area of the left ventricle, which were considered to be a consequence of side branch stenosis instead of stent restenosis. The true false-positive rate of perfusion defects was very low in the studied patients (*6*). The data emphasize that careful correlation of scintigraphic and angiographic information is necessary to maximize diagnostic test performance.

There were four cases in our population with a stent restenosis between 50% and 75% but with no reversible pattern of tracer distribution in the corresponding vascular territory. In four patients in our population, with a similar severity of stent restenosis, a reversible perfusion abnormality was detected by scintigraphy. The appropriate choice of cutoff values for defining hemodynamically significant restenosis remains subject to controversy. To be compatible with the recently published coronary angiographic studies evaluating stent restenosis (*9–12*), we used 50% instead of 75% for defining stent restenosis.

Evaluating any diagnostic test used in the clinical routine may be influenced by referral bias. This is due to a higher frequency of invasive controls after abnormal test results than after normal results. To reduce this effect in our study, we included most patients prospectively as part of a routine follow-up. The analysis of this subpopulation did not show any difference when compared to the whole population.

Study Limitations

One study limitation was the use of different stress methods. However, the parallel application of exercise and pharmacological stresses to evaluate myocardial perfusion reserve is widely accepted (*18,25*). For patients who cannot exercise, pharmacological stress provides more reliable test results than ineffective exercise (*18,25*). In our population, the most appropriate test was selected for each patient.

All images in this study were analyzed by qualitative evaluation, which may be considered a study limitation. The main advantage of quantitative analysis over the qualitative interpretation of experienced observers is the reduced intra-and inter-observer variability (*26,27*), which allows better detection of small changes of myocardial perfusion (i.e., effectiveness of therapy). In this study, our purpose was determining the effectiveness of the most commonly applied clinical approach, which is visual interpretation.

An additional limitation of our study was that it did not include data from patients early after coronary stent implantation. Our reasons for limiting our study to the chronic phase after stent implantation were suspected differences in the development of acute and chronic stent restenosis that may lead to different scintigraphic appearances of restenosis (transient or persistent defect) and the reported high false-positive rate of perfusion scintigraphy in the acute phase after percutaneous transluminal coronary angioplasty (*28,29*). To determine whether the transient deterioration of coronary reserve is present also in patients with implanted coronary stents, further studies are required with appropriate adjusted time intervals between angiographic and scintigraphic investigations.

CONCLUSION

Using stress-induced perfusion defects with reversibility at rest as the criterion on stress perfusion SPECT, chronic restenoses of coronary artery stents can accurately be detected. The sensitivity of the test is limited in vascular territories with a previous myocardial infarction. The perfusion abnormalities induced by stenoses of the side branch arteries should be considered; however, side branch stenoses induced by coronary stents are relatively infrequent.

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