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 201Tl perfusion scintigraphy (1), 15O-water positron emission tomography (PET) (2), Doppler catheter flow measurement (2,3) and quantitative cine angiography (4,5) have demonstrated sustained abnormalities in coronary flow reserve during the first days after percutaneous transluminal coronary angio-

plasty (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...
Coronary Flow Reserve After Stenting

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Abbreviations 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 \(^{160}\text{p,}\alpha\) 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 the basal-lateral and distal-lateral territories to the right coronary artery (RCA) 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
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 1. Clinical and Coronary Angiographic Data in 14 Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yrs)</th>
<th>Stented Artery</th>
<th>Reference Artery</th>
<th>Artery Not Involved in the Evaluation</th>
<th>Before Stenting</th>
<th>After Stenting</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39</td>
<td>LAD</td>
<td>LCX</td>
<td>RCA</td>
<td>0.9 (73)</td>
<td>2.7 (18)</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>RCA, LAD, LCX</td>
<td>no</td>
<td>RCA</td>
<td>0.6 (74)</td>
<td>3.2 (−3)</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>RCA</td>
<td>LAD</td>
<td>LCX</td>
<td>0.4 (86)</td>
<td>3.2 (−10)</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>LAD</td>
<td>RCA</td>
<td>RCX</td>
<td>0.7 (79)</td>
<td>3.2 (11)</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>LAD</td>
<td>RCA</td>
<td>RCX</td>
<td>0.5 (83)</td>
<td>3.0 (3)</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>LAD</td>
<td>LCX</td>
<td>RCA</td>
<td>1.2 (65)</td>
<td>3.2 (6)</td>
</tr>
<tr>
<td>7</td>
<td>49</td>
<td>RCA, LAD, LCX</td>
<td>no</td>
<td>RCA</td>
<td>0.7 (77)</td>
<td>3.3 (−3)</td>
</tr>
<tr>
<td>8</td>
<td>72</td>
<td>RCA</td>
<td>LAD</td>
<td>RCX</td>
<td>1.2 (63)</td>
<td>3.8 (12)</td>
</tr>
<tr>
<td>9</td>
<td>50</td>
<td>LAD</td>
<td>RCA</td>
<td>RCX</td>
<td>1.3 (59)</td>
<td>3.0 (3)</td>
</tr>
<tr>
<td>10</td>
<td>72</td>
<td>LCX</td>
<td>RCA, LAD, RCA</td>
<td>no</td>
<td>0.5 (83)</td>
<td>3.1 (−3)</td>
</tr>
<tr>
<td>11</td>
<td>67</td>
<td>LAD</td>
<td>RCA, LCX</td>
<td>no</td>
<td>1.0 (64)</td>
<td>3.2 (9)</td>
</tr>
<tr>
<td>12</td>
<td>56</td>
<td>RCA</td>
<td>LCX</td>
<td>LAD</td>
<td>1.1 (62)</td>
<td>3.5 (0)</td>
</tr>
<tr>
<td>13</td>
<td>66</td>
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<td>RCA, LCX</td>
<td>no</td>
<td>1.0 (68)</td>
<td>3.1 (3)</td>
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<tr>
<td>14</td>
<td>55</td>
<td>LAD</td>
<td>LCX</td>
<td>LAD</td>
<td>0.8 (73)</td>
<td>3.0 (6)</td>
</tr>
</tbody>
</table>

Mean: 59.1 ± 8.4

*p* values versus before stenting:

Mean: 0.85 ± 0.25

SD: 72.1 ± 17.7

*p* values versus remote:

0.0001 < 0.0001

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

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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Remote Area</th>
<th>Stented Area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest Flow</td>
<td>Adenosine Flow</td>
</tr>
<tr>
<td>1</td>
<td>62</td>
<td>199</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>212</td>
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<tr>
<td>3</td>
<td>78</td>
<td>196</td>
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<td>54</td>
<td>88</td>
</tr>
<tr>
<td>14</td>
<td>79</td>
<td>157</td>
</tr>
</tbody>
</table>

Mean: 76.1 ± 18.5

SD: 179.4 ± 47.4

*p* values versus remote:

0.89 ± 0.55

0.89 ± 0.55

CR = coronary reserve.
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
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 sequelae 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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