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Delayed Recovery of Coronary Resistive Vessel Function After Coronary Angioplasty

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Objectives. The aim of this study was to use Doppler catheterization and sequential dynamic positron emission tomography (PET) to investigate the role and time course of abnormal coronary resistive vessel function in the impairment of the coronary vasodilator response (maximal/basal coronary blood flow) after successful coronary angioplasty.

Background. The coronary vasodilator response may be impaired immediately after coronary angioplasty, despite successful dilation of a flow-limiting stenosis.

Methods. Twelve men (mean age 52 ± 10 years) with single-vessel coronary artery disease and normal left ventricular function were studied. The coronary vasodilator response to intravenous dipyridamole (0.5 mg·kg^{-1} over 4 min) was determined from intracoronary Doppler measurement of coronary flow velocity, before and after successful angioplasty. Basal and maximal myocardial blood flow in the angioplasty region and a normal region were determined in nine patients with positron emission tomography with $H_2{}^{15}O$ at 1 day (PET_1), 7 days (PET_2) and 3 months (PET_3) after angioplasty.

Results. The coronary vasodilator response, measured by Doppler catheterization, was similar before and immediately after angioplasty, 1.63 ± 0.41 and 1.62 ± 0.55, respectively (p = NS). After angioplasty, in seven of nine patients without restenosis, basal myocardial blood flow at PET_1, PET_2 and PET_3 was 0.98 ± 0.16, 0.94 ± 0.09 and 0.99 ± 0.13 ml·min^{-1}·g^{-1}, respectively, in the remote region and 1.19 ± 0.23 (p < 0.01 vs. remote region), 1.17 ± 0.19 (p < 0.01 vs. remote region) and 1.10 ± 0.08 ml·min^{-1}·g^{-1} (p = NS vs. remote region), respectively, in the angioplasty region. Myocardial blood flow after dipyridamole at PET_1, PET_2 and PET_3 was 3.04 ± 0.68, 3.00 ± 0.71 and 3.00 ± 0.60 ml·min^{-1}·g^{-1}, respectively, in the remote region and 2.11 ± 0.80 (p < 0.01 vs. remote region), 2.28 ± 0.73 (p = NS vs. remote region) and 3.06 ± 0.86 ml·min^{-1}·g^{-1} (p = NS vs. remote region), respectively, in the angioplasty region. The coronary vasodilator response at PET_1, PET_2 and PET_3 was 3.15 ± 0.85, 3.18 ± 0.68 and 3.08 ± 0.75, respectively, in the remote region and 1.80 ± 0.68 (p < 0.01 vs. remote region), 1.94 ± 0.49 (p < 0.01 vs. remote region) and 2.77 ± 0.74 (p = NS vs. remote region), respectively, in the angioplasty region.

Conclusions. After successful angioplasty, basal myocardial blood flow is increased for ≥7 days in the angioplasty region, with a reduction in the dipyridamole-induced increase in maximal myocardial blood flow for ≥24 h after the procedure. Thus, the coronary vasodilator response is impaired for ≥7 days after angioplasty, indicating that there is abnormal resistive vessel function in the coronary vascular bed distal to a coronary artery stenosis that persists for 7 days to 3 months.

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Animal studies indicate that dilation of the coronary resistive vessels can allow coronary blood flow to increase three to four times above rest values, even in the presence of a 70% diameter stenosis (1). However, in patients with coronary artery disease, the behavior of resistive vessels may be abnormal, and the ischemic threshold can be altered by changes in vasomotor tone at the level of the resistive vessels rather than in the large epicardial coronary arteries (2). At present, determining the contribution of resistive vessel dysfunction to myocardial blood flow limitation is problematic because it is impossible to separate the effects of altered vasomotion at the site of a flow-limiting coronary artery stenosis from those of the resistive vessels on modulation of the residual coronary blood flow (3,4).

To resolve the difficulty in establishing to what extent coronary blood flow can be modulated by resistive vessel dysfunction, it is necessary to evaluate coronary and regional myocardial blood flow in a clinical model of coronary artery disease that allows exclusion of the effect of a flow-limiting epicardial stenosis, such as after successful percutaneous transluminal coronary angioplasty. In addition, because the coronary vasodilator response may vary among patients, it is essential to compare, in each case, the behavior of the vascular bed distal to the stenosis with that of a remote myocardial territory. We used positron emission tomography (PET) to compare the results of Doppler catheter study of a myocardial region previously subtended by a

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coronary artery stenosis with a remote region subtended by an angiographically normal artery, and to monitor the coronary vasodilator response to dipyridamole (5,6) noninvasively. We report the changes in basal myocardial blood flow and the myocardial blood flow response to dipyridamole after angioplasty, together with the time course of these changes from 1 day up to 3 months after the procedure in diseased and remote myocardial regions.

Methods

Study Patients

Twelve men (mean age 52 ± 10 years, range 39 to 72) with chronic stable angina were studied. All patients had a positive exercise test response. Patients who had had a previous myocardial infarction or unstable angina pectoris were excluded. All had proximal left anterior descending coronary artery disease and were undergoing routine coronary angioplasty. The left circumflex and right coronary arteries were angiographically normal. Doppler catheter study was used to evaluate basal and postdipyridamole coronary blood flow velocity before and immediately after angioplasty in 12 patients; in 9 of these patients, PET scanning was used to evaluate regional basal and postdipyridamole myocardial blood flow 1 day, 7 days and 3 months after angioplasty.

Study Protocol

The protocol was approved by the Research Ethics Committee of Hammersmith Hospital and all patients gave informed and written consent.

All antianginal medication (except sublingual nitroglycerin) was discontinued at least 48 h before initial exercise testing and angioplasty and 72 h before PET scanning. No patient took nitroglycerin within 12 h of any part of the protocol. Treadmill exercise testing was performed according to the modified Bruce protocol the day before angioplasty. Coronary angioplasty was performed as clinically indicated. Coronary blood flow velocity and the coronary vasodilator response (defined as postdipyridamole coronary flow velocity/basal coronary flow velocity) (7) was measured before and after angioplasty, as described later. Positron emission tomographic scanning with measurement of the myocardial blood flow and coronary vasodilator response was undertaken 1 day after angioplasty (PET_1) in nine patients (three patients declined to continue in the study after angioplasty). Repeat exercise testing and PET scanning were performed at 7 ± 1 days (PET_2) and 100 ± 20 days (PET_3) after angioplasty, according to the same protocol as before. In all nine patients, repeat coronary angiography was performed at 110 ± 25 days.

1. Coronary blood flow velocity measurement by Doppler catheterization. Coronary angiography was performed as clinically indicated to best demonstrate the lesion morphology. On completion, an 8F guiding catheter was inserted into the left coronary ostium. A 0.010- or 0.012-in. (0.025 or 0.03 cm) "Hi-Torque" guide wire (Advanced Cardiovascular Systems) was advanced across the coronary lesion in the usual fashion. Provided there was no evidence of myocardial ischemia (chest pain or electrocardiographic [ECG] changes), a 3F Doppler flow catheter (model DC 201, Millar Instruments) with a 20-MHz pulsed Doppler crystal, referenced to zero and calibrated, was advanced over the guide wire. The tip of the Doppler catheter was positioned up to 5 mm proximal to the stenosis (8). The Doppler velocimeter range control was adjusted to obtain an optimal audio signal and both phasic and mean tracings of maximal coronary blood flow velocity at rest.

Coronary flow velocity, heart rate and systemic arterial pressure were measured continuously. Resistive vessel dilation was induced by dipyridamole (0.5 $mg \cdot kg^{-1}$ intravenously over 4 min). In seven patients, coronary flow velocity was measured before coronary angioplasty. Angioplasty was then performed entirely as clinically indicated with an Advanced Cardiovascular Systems RX balloon angioplasty catheter. After the procedure, the angioplasty catheter was removed, leaving the guide wire in place. The Doppler flow catheter was repositioned as before. Repeat measurements of basal and maximal coronary blood flow velocity after dipyridamole were performed as described before in all 12 patients.

Quantitative coronary arteriography. Coronary arteriograms were analyzed by an automated edge contour detection computer analysis system (Cardiovascular Angiographic Analysis System [CAAS]) (9). The lumen diameter of both the coronary stenosis, in the projection showing maximal severity, and the proximal reference segment was measured at end-diastole with care taken to select a view free from overlapping vessels. This measurement was performed under basal conditions and at the peak effect on coronary flow velocity of dipyridamole both before and after angioplasty. The diameter of the stem of the Judkins coronary catheter was used for calibration to obtain measurements in absolute units (mm). Correction was made for radiographic pincushion distortion. Stenosis severity was also expressed as percent reduction of the internal lumen diameter relative to the angiographically normal proximal coronary segment, the reference segment. Restenosis was defined with the criteria used by Beatt et al. (10): a reduction in the residual lumen diameter ≥0.72 mm and ≥50% diameter stenosis.

Calculation of coronary vascular resistance index. The coronary vascular resistance index was calculated as the quotient of mean arterial pressure and coronary blood flow velocity and expressed in units (11).

2. Regional myocardial blood flow measurement with positron emission tomography. Regional myocardial blood flow was measured with the use of oxygen-15 (^{15}O) and dynamic PET scanning (12), which was performed at three time points after coronary angioplasty in nine patients: 1) within 24 h, 2) at 7 ± 1 days, and 3) at 100 ± 20 days. All

PET scans were recorded with an ECAT 931-08/12 scanner (CTI Inc.). The scanner consists of eight contiguous rings of bismuth germanate detectors, which allows 15 cross-sectional images of the heart to be visualized simultaneously in a 10.5-cm axial field of view. All emission scans were reconstructed with a Hanning filter that had a cutoff frequency of half maximum. This resulted in a transaxial resolution of 8.4 ± 0.7 mm FWHM (full width at half maximum) for the emission data at the center of the field of view (13). Thus, it was possible to record simultaneously myocardial and blood tracer concentrations of the whole heart.

Scanning procedure. Patients abstained from drinking tea or coffee on the morning of the PET scan and all had taken no antianginal medication for ≥72 h. After angioplasty, patients were treated with intravenous nitrate until 12 h before the scan.

Patients were positioned in the scanner and a 5-min rectilinear transmission scan was recorded to allow positioning of the left ventricle in the center of the field of view. This was done by exposing a circular ring source using 2 mCi of germanium-68. Another transmission scan, recorded for 20 min, was used to correct all emission scans for tissue attenuation. The patient's position with respect to the camera was determined by a cross-shaped low power laser beam and pen marks on the patient's skin. After transmission, radioactive gases were continuously delivered by an MC face mask. Blood pool scans were performed with ^{15}O-labeled carbon monoxide ($C^{15}O$). This tracer, which forms ^{15}O-carboxyhemoglobin, was continuously delivered at a flow rate of 500 ml·min^{-1} (3 MBq·ml^{-1}) for 4 min, and a 6-min single-frame scan was recorded starting 1 min after the end of gas delivery. Venous blood samples were taken before and after gas delivery. The $C^{15}O$ concentration was measured with a sodium iodide well counter cross-calibrated with the scanner. After a 10-min period to allow for decay, a continuous inhalation of $C^{15}O_2$ was given for 3.5 min (4 MBq·ml^{-1} at a flow rate of 500 ml·min^{-1}). The $C^{15}O_2$ is converted immediately by the enzyme carbonic anhydrase in the lung capillaries to ^{15}O-labeled water ($H_2{}^{15}O$), which is delivered to pulmonary venous blood (14). A sequence of 24 scans, starting with $C^{15}O_2$ delivery, consisted of six scans of 5, 10, 20 and 30 s, producing a build-up scan over 3.5 min and a washout scan over 3 min.

Basal myocardial blood flow was measured in all patients. After 10 min to allow for decay, the myocardial blood flow was measured after an intravenous infusion of dipyridamole (0.5 mg·kg^{-1} over 4 min). The delivery of $C^{15}O_2$ started 2 min after the end of this infusion. A standard 12-lead ECG was recorded every minute during the dipyridamole infusion and for up to 8 min after the infusion. Blood pressure was measured every minute by a cuff sphygmomanometer during the same period of time.

Analysis of PET data. The sinograms were corrected for attenuation and reconstructed on a Microvax II computer (Digital Equipment Corporation) with the use of dedicated array processors and standard reconstruction algorithms (12,13). Images were transferred to a SUN 3/60 work station for further analysis with Analyze (Mayo Foundation) and Pro-Matlab (The Mathworks Inc.) software packages.

A blood volume image was created with the $C^{15}O$ data by dividing the raw image by the product of the average venous blood radioactivity and the density of whole blood (1.06 g·ml^{-1}). Either four or five transaxial regions of interest were drawn within the left atrium and projected onto the dynamic $H_2{}^{15}O$ images to generate time-activity curves for each region. The average was used as arterial input function. Images of extravascular volume were created by subtracting blood volume from transmission images after the latter were normalized for tissue density (1.04 g·ml^{-1}). In addition, the blood volume images were subtracted from the integrated time frames of the washout phase of the $H_2{}^{15}O$ studies. The images of extravascular volume and extravascular $H_2{}^{15}O$ were used to delineate four regions of myocardium (anterior, lateral, inferoposterior and septal) over five to seven transaxial planes, and data were averaged before the modeling of myocardial perfusion. The regions of interest were superimposed onto the kinetic time frames recorded during the $C^{15}O_2$ inhalation and washout. This procedure generated for each region myocardial tissue time-activity curves that, together with arterial time-activity curves, were fitted to a single tissue compartment tracer kinetic model to give values for regional myocardial blood flow (in ml·min^{-1}·g^{-1}) (12).

In all patients, the anterior region was designated as the angioplasty region and the inferoposterior region as the remote region. Basal myocardial blood flow and myocardial blood flow after dipyridamole were determined in both regions. The coronary vasodilator response was defined as myocardial blood flow after dipyridamole/basal myocardial blood flow (7).

Statistical analysis. All values are expressed as mean value ± SD. Data from Doppler catheter study before and after angioplasty were analyzed with the paired Student *t* test. Two-way analysis of variance (ANOVA) was used to compare data derived from PET scanning at the different time intervals. Specific comparisons were done using the paired Student *t* test corrected for multiple comparisons with the Bonferroni inequality adjustment (15). Linear regression analysis was used to examine the relation between coronary artery dimensions and the coronary vasodilator response measured by Doppler flow catheter. Myocardial blood flow values in the regions of interest in each individual plane for each scan were derived and the coefficient of variation within and between groups was measured by one-way ANOVA. A p value < 0.05 was considered statistically significant.

Results

Doppler flow catheter study was performed in 7 patients before angioplasty and in all 12 patients after angioplasty

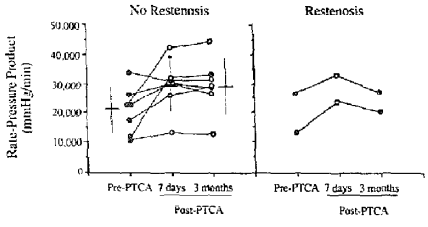

Figure 1. Exercise testing before (Pre), at 7 days and at 100 days after (Post) angioplasty (PTCA) in two patients with and in seven without restenosis. *$p < 0.05$ versus value before angioplasty. ○ = no significant ST segment depression; ● = ≥0.1 mV ST segment depression.

(see Table 2). A PET scan was obtained 1 day after angioplasty in nine patients (three patients declined to continue in the study after angioplasty). Seven days (mean 7 ± 1) and 3 months (mean 100 ± 20 days) after angioplasty, the same nine patients underwent repeat exercise testing and PET scanning, according to the protocol used before (see Tables 4 and 5). In all nine patients, repeat coronary angiography was performed 110 ± 25 days after the initial angioplasty procedure. Two patients who had developed recurrent angina and who had a positive exercise test at this time had restenosis of the dilated arterial segment, as defined earlier.

Exercise testing (Fig. 1). Before angioplasty, all patients underwent treadmill exercise testing after at least 48 h without antianginal medication. Nine patients agreed to continue in the study after angioplasty. Before angioplasty, the rate-pressure product was 9,160 ± 2,880 mm Hg·min^{-1} at rest, 18,310 ± 7,820 mm Hg·min^{-1} at 0.1-mV ST segment depression and 20,750 ± 7,670 mm Hg·min^{-1} at peak exercise. Seven days after angioplasty, all nine patients had a negative exercise test response; rate-pressure product at peak exercise was 29,410 ± 7,920 mm Hg·min^{-1} ($p < 0.05$ vs. peak rate-pressure product before angioplasty). In the seven patients with no restenosis, rate-pressure product at peak exercise was 20,960 ± 7,830 mm Hg·min^{-1} before angioplasty and 29,550 ± 8,690 mm Hg·min^{-1} at 7 days ($p < 0.05$ vs. peak rate-pressure product before angioplasty). All nine patients underwent exercise testing approximately 3 months (mean 100 ± 20 days) after angioplasty. The exercise test response was negative in six patients and positive in three. Of these three patients, two had restenosis; one asymptomatic patient without restenosis (Patient 3) reached 0.1-mV ST segment depression at a rate-pressure product of 25,830 mm Hg·min^{-1} (vs. 8,370 mm Hg·min^{-1} before angioplasty), unassociated with symptoms of chest pain. Thus, the rate-pressure product at peak exercise in the seven patients without restenosis was 29,560 ± 9,310 mm Hg·min^{-1}.

The two patients with restenosis at 3 months had a negative test response at 7 days. Patient 8 had a rate-pressure product to 0.1-mV ST segment depression of 18,600 mm Hg·min^{-1} at 3 months (vs. 9,960 mm Hg·min^{-1} before angioplasty), and Patient 9 had a rate-pressure product to 0.1-mV ST segment depression of 21,450 mm Hg·min^{-1} at 3 months (vs. 21,250 mm Hg·min^{-1} before angioplasty) (Fig. 1).

Quantitative coronary arteriography (Table 1). There was an increase in lumen diameter at the site of stenosis from 0.64 ± 0.28 mm before angioplasty to 1.86 ± 0.48 mm ($p < 0.0001$) immediately after angioplasty, corresponding to a reduction in percent lumen stenosis severity from 73.1 ± 10.3% to 26.2 ± 7.2% ($p < 0.0001$).

Before angioplasty, at the peak effect of dipyridamole, there was no significant change in diameter at the stenosis or of the reference segment: 0.74 ± 0.27 and 2.29 ± 0.38 mm, respectively. After angioplasty, there was no significant change in diameter at the stenosis, 1.86 ± 0.48 and 1.84 ± 0.46 mm, or of the reference segment, 2.50 ± 0.50 and 2.54 ± 0.39 mm, from basal state to peak dipyridamole, respectively.

At follow-up arteriography, there was no evidence of restenosis in seven patients, with a lumen diameter at the site of stenosis of 1.80 ± 0.23 mm (p = NS vs. postangio-

Table 1. Quantitative Coronary Arteriographic Findings in 12 Patients

	Basal State	Peak Dipyridamole Effect
Before angioplasty		
Stenosis (mm)	0.64 ± 0.28	0.74 ± 0.27
Reference (mm)	2.50 ± 0.57	2.29 ± 0.38
% stenosis	73.1 ± 10.3%	67.6 ± 8.9%
After angioplasty		
Stenosis (mm)	1.86 ± 0.48*	1.84 ± 0.46*
Reference (mm)	2.50 ± 0.50	2.54 ± 0.39
% stenosis	26.2 ± 7.2%*	27.8 ± 13.1%*
Follow-up arteriography†		
Stenosis (mm)	1.80 ± 0.23	—
Reference (mm)	2.61 ± 0.36	—
% stenosis	29.6 ± 16.0%	—

*$p < 0.0001$ versus value before angioplasty. †Data are from the seven patients without restenosis among the nine patients who underwent follow-up coronary arteriography.

Table 2. Doppler Coronary Flow Velocity

	Before Angioplasty (n = 7)			After Angioplasty (n = 12)		
Pt. No.	Basal State	Peak Dipyridamole Effect	Coronary Vasodilator Response	Basal State	Peak Dipyridamole Effect	Coronary Vasodilator Response
1	4.3	9.2	2.14	4.0	11.0	2.75
2	15.5	15.5	1.00	22.0	27.0	1.23
3	—	—	—	12.0	15.0	1.25
4	—	—	—	6.0	7.5	1.25
5	7.0	12.0	1.71	7.5	9.0	1.20
6	4.6	6.8	1.48	6.0	8.8	1.47
7	5.9	12.2	2.07	7.4	14.3	1.93
8	—	—	—	10.0	17.8	1.78
9	—	—	—	7.0	11.2	1.6
10	—	—	—	5.6	12.5	2.23
11	5.8	7.6	1.31	8.0	10.8	1.35
12	9.2	15.8	1.72	14.6	20.8	1.42
Mean	7.5	11.3	1.63	9.2	13.8	1.62
SD	3.9	3.6*	0.41	5.0	5.7†	0.48

*$p < 0.01$, †$p < 0.001$ versus basal state.

plasty stenosis diameter) and a reference diameter of 2.61 ± 0.36 mm (p = NS vs. postangioplasty reference diameter). Two patients had evidence of restenosis: a residual lumen diameter of 0.46 mm (reference diameter of 3.11 mm) in Patient 8 and complete occlusion at the site of previous angioplasty in Patient 9. In Patient 9, there was no clinical or ECG evidence of myocardial infarction.

Coronary flow velocity determined by Doppler catheter (Table 2, Fig. 2 and 3). Seven patients underwent Doppler catheterization before angioplasty (Table 2). Heart rate increased from 64 ± 8 beats·min^{-1} at basal state to 82 ± 5 beats·min^{-1} at the peak effect of dipyridamole ($p < 0.01$), with no significant reduction in systolic (149 ± 18 to 140 ± 15 mm Hg), diastolic (92 ± 9 to 87 ± 10 mm Hg) or mean (111 ± 11 to 106 ± 11 mm Hg) arterial pressure. Coronary flow velocity increased from a basal value of 7.5 ± 3.9 cm·s^{-1} to 11.3 ± 3.6 cm·s^{-1} ($p < 0.01$) after dipyridamole, with a coronary vasodilator response of 1.63 ± 0.41 (Fig. 2). The coronary vascular resistance index decreased from 17.5 ± 6.4 U at basal state to 10.1 ± 3.2 U ($p < 0.01$) with dipyridamole (Fig. 3).

Twelve patients underwent Doppler catheterization after angioplasty (Table 2). Heart rate increased from 66 ± 13 beats·min^{-1} at basal state to 81 ± 18 beats·min^{-1} at the peak effect of dipyridamole ($p < 0.001$), with no significant reduction in systolic (135 ± 21 mm Hg to 130 ± 20 mm Hg),

Figure 2. Bar graphs showing coronary flow velocity at basal state and at peak dipyridamole (Dip) effect in seven patients before angioplasty and seven patients after angioplasty. *$p < 0.05$ versus value before angioplasty. **$p < 0.01$ versus value in basal state. Abbreviations as in Figure 1.

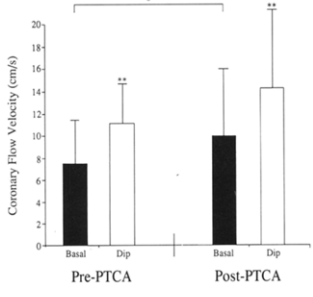

Figure 3. Bar graphs showing coronary vascular resistance index at basal and at peak dipyridamole (Dip) effect in seven patients before angioplasty and seven patients after angioplasty. *$p < 0.05$ versus value before angioplasty. **$p < 0.01$ versus value in basal state. Abbreviations as in Figure 1.

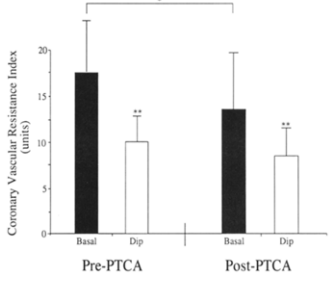

Table 3. Hemodynamic Variables at Positron Emission Tomography

Study	Basal State				Peak Dipyridamole Effect			
	Heart Rate (beats/min)	Systolic Blood Pressure (mm Hg)	Diastolic Blood Pressure (mm Hg)	Rate-Pressure Product (mm Hg·min^{-1})	Heart Rate (beats/min)	Systolic Blood Pressure (mm Hg)	Diastolic Blood Pressure (mm Hg)	Rate-Pressure Product (mm Hg·min^{-1})
PET_1	62 ± 12	120 ± 11	73 ± 13	7,590 ± 1,440	78 ± 16	127 ± 19	75 ± 13	9,860 ± 2,550
PET_2	61 ± 9	123 ± 10	76 ± 10	7,590 ± 1,460	79 ± 13	128 ± 14	76 ± 8	10,190 ± 2,480
PET_3	66 ± 7	120 ± 14	80 ± 7	7,860 ± 1,380	82 ± 10	130 ± 13	78 ± 8	10,890 ± 2,110

PET_1, PET_2, PET_3 = positron emission tomographic scan at 1 day, 7 days and 3 months, respectively, after angioplasty.

diastolic (94 ± 10 to 87 ± 12 mm Hg) or mean (100 ± 12 to 96 ± 15 mm Hg) arterial pressure. The basal coronary flow velocity was 9.2 ± 5.0 cm·s^{-1} and the maximal coronary flow velocity at peak dipyridamole effect was 13.8 ± 5.7 cm·s^{-1} ($p < 0.001$ vs. basal value). The coronary vascular resistance index decreased from 13.2 ± 5.2 U at basal state to 7.8 ± 2.8 U with dipyridamole ($p < 0.01$ vs. basal state), with a coronary vasodilator response of 1.62 ± 0.48. With linear regression analysis, no relation was demonstrated between residual stenosis diameter after angioplasty and the coronary vasodilator response.

Coronary flow velocity and coronary vascular resistance were compared in the seven patients who were studied before and after angioplasty. In these seven patients, the mean interval between the start of each dipyridamole infusion was 55.6 ± 10.6 min. There were no significant differences in systolic, diastolic or mean arterial pressures at basal state or at peak dipyridamole effect before or after angioplasty. After angioplasty, the basal coronary blood flow velocity was significantly increased to 9.9 ± 6.2 cm·s^{-1} ($p < 0.05$ vs. basal value before angioplasty) although the velocity after dipyridamole, 14.5 ± 6.9 cm·s^{-1}, was not significantly changed (p = NS vs. peak dipyridamole before angioplasty) (Fig. 2). After angioplasty, the coronary vasodilator response was 1.62 ± 0.55 (p = NS vs. before angioplasty). The basal coronary vascular resistance index was significantly lower after angioplasty, 13.6 ± 6.2 U ($p < 0.05$ vs. basal state before angioplasty), although the value at peak dipyridamole, 8.3 ± 3.1 U, was similar to that before angioplasty (p = NS vs. peak dipyridamole before angioplasty) (Fig. 3).

Myocardial blood flow determined by positron emission tomography (Tables 3 to 5, Fig. 4 and 5). Heart rate, systolic and diastolic blood pressure and rate-pressure product at basal state and at peak dipyridamole effect at each PET study are shown in Table 3. There were no significant differences in these hemodynamic variables comparing all three studies. Individual myocardial blood flow data at basal state and at peak dipyridamole effect and the coronary vasodilator response at 1 day, 7 days and 3 months are shown in Tables 4 and 5.

One day after angioplasty, in the seven (of nine) patients without restenosis at 3 months, myocardial blood flow at rest was significantly higher in the anterior (angioplasty) region, 1.19 ± 0.23 ml·min^{-1}·g^{-1}, than in the inferoposterior (remote) region, 0.98 ± 0.16 ml·min^{-1}·g^{-1} ($p < 0.01$) (Fig. 4). This increase in basal myocardial blood flow was still

Table 4. Regional Myocardial Blood Flow at Positron Emission Tomography

Pt No.	PET_1				PET_2				PET_3			
	Angioplasty Region		Remote Region		Angioplasty Region		Remote Region		Angioplasty Region		Remote Region	
	Basal	Dipyr	Basal	Dipyr	Basal	Dipyr	Basal	Dipyr	Basal	Dipyr	Basal	Dipyr
Patients Without Restenosis at Follow-Up Angiography												
1	1.24	1.43	1.14	3.01	1.46	3.54	1.11	2.81	1.22	3.90	0.89	3.38
2	1.06	1.38	0.92	1.87	0.97	1.36	0.80	1.92	1.04	1.63	0.78	2.10
3	0.84	2.14	0.74	3.22	1.07	2.65	0.98	3.93	1.01	3.72	0.96	3.89
4	1.20	1.45	0.85	3.48	1.29	1.68	0.96	3.63	1.05	3.38	0.95	2.97
5	1.19	2.05	1.04	2.59	1.00	1.80	0.92	2.38	1.04	2.15	1.14	2.40
6	1.60	2.81	1.08	3.11	1.06	2.50	0.90	3.40	1.19	3.03	0.87	3.09
7	1.21	3.50	1.15	4.02	1.33	2.43	0.94	2.96	1.15	3.58	1.20	3.15
Mean	1.19	2.11	0.98	3.04	1.17	2.28	0.94	3.00	1.10	3.06	0.99	3.00
SD	0.23*	0.80*	0.16	0.68	0.19*	0.73	0.09	0.71	0.08	0.86	0.13	0.60
Patients With Restenosis at Follow-Up Angiography												
8	1.46	1.86	0.74	2.33	0.9	1.42	0.79	1.19	0.82	1.05	0.84	0.91
9	1.60	1.81	1.00	3.61	1.10	1.34	0.79	2.78	0.78	1.48	0.69	1.26

*$p < 0.01$ versus value in the remote region. 1 day (PET_1), 7 days (PET_2), and 3 months (PET_3) after successful coronary angioplasty in the seven patients without restenosis at follow-up angiography. Basal = basal state; Dipyr = peak dipyridamole effect; other abbreviations as in Table 3.

Table 5. Coronary Vasodilator Response at Positron Emission Tomography

Pt No.	PET_1		PET_2		PET_3	
	Angioplasty Region	Remote Region	Angioplasty Region	Remote Region	Angioplasty Region	Remote Region
Patients Without Restenosis at Follow-Up Angiography						
1	1.15	2.64	2.42	2.53	3.20	3.80
2	1.30	2.03	1.40	2.40	1.57	2.36
3	2.55	4.35	2.48	4.01	3.68	4.05
4	1.21	4.09	1.30	3.78	3.22	3.11
5	1.72	2.56	1.80	2.59	2.07	2.11
6	1.76	2.88	2.36	3.78	2.55	3.55
7	2.89	3.50	1.83	3.15	3.11	2.62
Mean	1.80	3.15	1.94	3.18	2.77	3.08
SD	0.68*	0.85	0.49*	0.68	0.74	0.75
Patients With Restenosis at Follow-Up Angiography						
8	1.27	3.01	1.58	1.51	1.28	1.08
9	1.13	3.61	1.22	3.52	1.90	1.83

*$p < 0.01$ versus remote region. Individual coronary vasodilator responses in the angioplasty and remote regions, 1 day (PET_1), 7 days (PET_2) and 3 months (PET_3) after successful coronary angioplasty in the seven patients without restenosis at follow-up angiography. The individual values for the two patients with restenosis are given for comparison.

present 7 days after angioplasty: 1.17 ± 0.19 ml·min^{-1}·g^{-1} in the angioplasty region compared with 0.94 ± 0.09 ml·min^{-1}·g^{-1} in the remote region ($p < 0.01$). Three months after angioplasty, there was no significant difference between basal myocardial blood flow in the angioplasty and remote regions (1.10 ± 0.08 and 0.99 ± 0.13 ml·min^{-1}·g^{-1}, respectively) (Table 4, Fig. 4).

The dipyridamole-induced increase in myocardial blood flow in the angioplasty region at 1 day, 2.11 ± 0.80 ml·min^{-1}·g^{-1}, was lower than that in the remote region, 3.04 ± 0.68 ml·min^{-1}·g^{-1} ($p < 0.01$). At 7 days, although the myocardial blood flow response to dipyridamole was still lower in the angioplasty region than in the remote region (2.28 ± 0.73 and 3.00 ± 0.71 ml·min^{-1}·g^{-1}, respectively), this was not a significant difference. At 3 months after angioplasty, the myocardial blood flow response to dipyridamole was similar in the angioplasty and remote regions (3.06 ± 0.86 and 3.00 ± 60 ml·min^{-1}·g^{-1}, respectively) (Table 4, Fig. 4).

One day after angioplasty, the coronary vasodilator response was significantly lower in the angioplasty region, 1.80 ± 0.68, than in the remote region, 3.15 ± 0.85 ($p < 0.01$) (Fig. 5). This difference was present 7 days after angioplasty: 1.94 ± 0.49 in the angioplasty region versus 3.18 ± 0.68 in the remote region ($p < 0.01$). Three months after angioplasty, the coronary vasodilator response was similar in the two regions: 2.77 ± 0.74 and 3.08 ± 0.75 (p = NS) in the angioplasty and remote regions, respectively.

In the two patients with restenosis at 3 months, there was an impaired coronary vasodilator response in the angioplasty region (1.28 in Patient 8 and 1.90 in Patient 9) compared with the mean value of 2.77 ± 0.74 in the seven patients without restenosis. In the remote region, the coronary vasodilator response was also impaired (1.08 in Patient 8 and 1.83 in

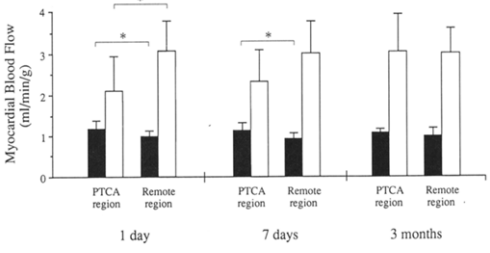

Figure 4. Bar graphs showing myocardial blood flow in the basal state and at dipyridamole effect in the angioplasty and remote myocardial regions at 1 day (PET_1), 7 days (PET_2) and 3 months (PET_3) after successful angioplasty (PTCA). *$p < 0.01$. ■ = basal state; □ = at peak dipyridamole effect.

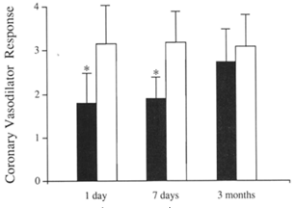

Figure 5. Bar graphs showing the coronary vasodilator response in the angioplasty and the remote myocardial regions at 1 day (PET_1), 7 days (PET_2) and 3 months (PET_3) after successful angioplasty. *$p < 0.05$. ■ = angioplasty region; □ = remote region.

Patient 9) compared with the mean value of 3.08 ± 0.75 in the seven patients without restenosis (Tables 4 and 5).

To assess variability in the myocardial blood flow measurements in the angioplasty and remote regions in individual planes at each scan, the coefficient of variation was measured. At basal state, the coefficient of variation was 21.3 ± 9.7%, 23.1 ± 12.6% and 22.3 ± 9.4% (all p = NS) in the angioplasty region and 24.9 ± 10.6%, 30.4 ± 9.8% and 28.7 ± 3.7% (all p = NS) in the remote region at PET_1, PET_2 and PET_3, respectively. After dipyridamole, the coefficient of variation in the angioplasty region was 23.8 ± 8.7%, 25.9 ± 10.8% and 24.7 ± 12.2% (all p = NS); in the remote region it was 30.5 ± 10.0%, 33.8 ± 5.5% and 36.1 ± 10.1% (all p = NS) at PET_1, PET_2 and PET_3, respectively. These coefficients of variation are similar to that reported previously (12).

Discussion

In this study, immediately after successful coronary angioplasty, despite a marked and significant reduction in stenosis severity, maximal coronary blood flow velocity at peak dipyridamole effect was similar to that observed before angioplasty, and the coronary vasodilator response remained unchanged. Basal coronary blood flow velocity in the region subtended by the stenosed artery before angioplasty was similar to that reported in normal subjects (8), and increased immediately after angioplasty. Measurement of basal myocardial blood flow showed that the increase persisted for at least 7 days in the angioplasty region after angioplasty, compared with values in the remote region, but by 3 months, it had returned to normal. The maximal myocardial blood flow response to dipyridamole in the angioplasty region was lower than that in the remote region 24 h after angioplasty, a finding consistent with the observations made immediately after angioplasty with the Doppler catheter, but by 7 days it had returned toward normal values. Thus, the coronary vasodilator response in the region subtended by the previously stenosed coronary artery is impaired for the 1st 24 h after angioplasty because of an increase in basal coronary blood flow and a reduction in the maximal vasodilator response. At 7 days, it is still impaired because of an increase in basal coronary blood flow although the maximal blood flow response to dipyridamole has returned toward normal.

Persistent reduction in the coronary vasodilator response after angioplasty. We were able to document a reduced coronary vasodilator response by both Doppler catheter and PET scanning. The PET study allowed us to show that the coronary vasodilator response was significantly lower in the angioplasty region than in the remote region for at least 1 week after successful angioplasty. The dipyridamole infusion induced an increase in myocardial blood flow and a coronary vasodilator response in the remote region similar to that previously described in patients with chronic stable angina and single-vessel coronary artery disease, although lower than the value usually reported in normal subjects (12). We (16) and others (17) have shown that the coronary vasodilator response to dipyridamole is lower in myocardium supplied by angiographically normal arteries in patients with single-vessel coronary artery disease and a normal left ventricle, compared with the response in patients without coronary artery disease. The value that we found in the remote region in the present study is similar to that reported before in patients with single-vessel disease (12).

Alleviation of the flow-limiting coronary artery stenosis would be expected to permit a larger coronary blood flow when resistive vessel dilation is induced. Our findings thus indicate that there was a clear failure of the resistive vessels to dilate in response to dipyridamole within the 1st 24 h. Furthermore, after angioplasty, there may have been residual effects of the first dose of dipyridamole on myocardial blood flow and this might be expected to augment the response to the second dose of dipyridamole. Thus, a possible explanation for the higher basal blood flow after angioplasty is that it was caused by the residual effects of the first dose of dipyridamole. This seems an unlikely explanation, however, because basal myocardial blood flow measured by PET revealed a higher value in the angioplasty region compared with the remote region for at least 7 days after angioplasty. A more striking finding was that the maximal increase in blood flow velocity in response to dipyridamole after angioplasty was not higher than the value before angioplasty, clearly indicating a failure of resistive vessel dilation.

Comparison with other studies. Several groups have described an impaired coronary vasodilator response after angioplasty (11,18–20). Wilson et al. (18) reported that the coronary vasodilator response to papaverine, measured by Doppler-guided catheter, was impaired immediately after angioplasty in 55% of patients, and that in these patients it had returned to normal by a mean follow-up period of 7.5 months. Zijlstra et al. (19) reported that the coronary vasodilator response to papaverine was similarly impaired in all

their patients immediately after angioplasty. Neither of these studies reported either basal or peak coronary blood flow or velocity, but only the coronary vasodilator response. Kern et al. (11) and Nanto et al. (20) reported an impaired coronary vasodilator response immediately after angioplasty because of both an increase in basal coronary blood flow and a decreased maximal coronary blood flow response to papaverine and atrial pacing, respectively. These reports are consistent with our study: basal coronary blood flow was increased immediately after angioplasty and thereafter for ≥7 days, and the maximal coronary blood flow response to dipyridamole was impaired immediately after angioplasty and for at least the 1st 24 h. The coronary vasodilator response was therefore reduced for at least the 1st 7 days after angioplasty. Laarman et al. (21) reported no change in the coronary vasodilator response to papaverine using digital subtraction angiography immediately after angioplasty and, as in our study, no correlation was shown between residual stenosis diameter and the impaired coronary vasodilator response.

Walsh et al. (22) used PET to measure the coronary vasodilator response after angioplasty, and reported that it returned to normal in all patients after the procedure, but this study was limited because individual patients were studied at different time intervals (range 1 to 18 days [mean 11]) after angioplasty with no serial studies. It is thus likely that any alterations in basal or maximal myocardial blood flow contributing to an abnormal coronary vasodilator response within the 1st week were missed. Nevertheless, these data are consistent with our study since we have shown that the coronary vasodilator response returns to normal between 7 days and 3 months. In studies using thallium-201 stress imaging, this delay in the recovery of perfusion has also been reported in patients persisting between 4 and 18 days after angioplasty (23).

Nienaber et al. (24) reported a reduction in "perfusion defects" in patients studied with PET within 72 h of angioplasty, implying an early recovery of myocardial perfusion, but this was a qualitative analysis with no quantification of myocardial blood flow or measurement of the vasodilator response, and hence it does not define the vasodilator abnormalities present in the angioplasty region relative to a remote region. Studies by Lassar et al. (25) and Hodgson et al. (26) reported that the coronary blood flow reserve measured in dilated vessels immediately after angioplasty was similar to that measured in normal coronary arteries. However, these studies are less reliable because the xenon-133 techniques tend to overestimate coronary flow, and because the stimulus for coronary vasodilation (iodinated contrast medium or small doses of papaverine) may have been variable.

Mechanisms for the alteration in resistive vessel function after angioplasty. Several vascular beds including the coronary circulation autoregulate arteriolar resistance according to perfusion pressure (27). The effects of a prolonged reduction in perfusion pressure (resulting from an epicardial coronary artery stenosis) on resistive vessel autoregulation are not well documented. It is possible that prolonged resistive vessel dilation resulting from a low perfusion pressure distal to the stenosis might cause a transient inability of these vessels to autoregulate in response to a sudden restoration of a normal perfusion pressure (28). If, after the abrupt restoration of a normal coronary perfusion pressure by successful angioplasty, the resistive vessels failed to vasoconstrict, then an increase in basal myocardial blood flow and a fall in the maximal myocardial blood flow/basal myocardial blood flow ratio, that is, the coronary vasodilator response, would be expected, as was observed in this study.

Alternatively, basal myocardial blood flow may have been elevated because of the release of vasoactive agents at the time of angioplasty—that is, from platelets activated by and adherent to the site of dilation, the injured vessel wall or even the myocardial cells themselves, perhaps as a result of transient ischemia. This is a less likely explanation because the increase in basal myocardial blood flow persisted for ≥7 days and factors directly related to the procedure would be expected to resolve by that time. It is more probable that resistive vessel function is abnormal before angioplasty because of the altered autoregulatory mechanisms to compensate for the stenosis, as discussed earlier.

The maximal myocardial blood flow response to dipyridamole was also reduced immediately after angioplasty. The mechanisms underlying this response are uncertain and several can be considered. Vasoconstrictor substances released by platelets at the angioplasty site may limit maximal vasodilation (29). Embolization of the distal coronary circulation with platelet aggregates or fragments of thrombus might result in transient alterations in coronary blood flow that later regress (30). One animal study has shown that microembolization of the coronary circulation increased coronary blood flow at rest and decreased the maximal hyperemic coronary blood flow response (31). Other factors related to the presence of a severe stenosis such as recurrent ischemia before and during angioplasty might have produced transient changes in the maximal coronary vasodilator response. Although it has been suggested that short-term administration of calcium channel blockers can reduce vasodilator capacity (32), which were avoided in our study, Wilson et al. (18) found no difference in the coronary vasodilator response in patients being treated with nitrates, beta-blockers and calcium channel blockers compared with those not taking antianginal medication.

Clinical implications. Two important clinical implications arise out of this study. 1) A satisfactory angiographic result does not indicate the immediate return of the behavior of the coronary circulation to normal. However, in the absence of restenosis, basal myocardial blood flow, the myocardial blood flow response to dipyridamole and, thus, the coronary vasodilator response will return to normal over a variable period of ≥1 week. This observation may account for the finding of a positive exercise test response several days after angioplasty in the absence of restenosis (33). Thus, exercise

tests and other noninvasive stress tests will be more reliable in detecting restenosis if performed ≥1 week after angioplasty. Conversely, measurement of the coronary vasodilator response after angioplasty cannot be used to assess the adequacy of the procedure because it may take several days before the response has normalized. 2) Resistive vessel function may be altered in patients with coronary artery disease. Immediately after removal of the stenosis by angioplasty, there is no improvement in coronary vasodilator response, suggesting that resistive vessel dysfunction in patients with coronary artery disease may contribute to the development of myocardial ischemia.

Conclusions. After successful angioplasty, basal myocardial blood flow is increased for ≥7 days in the myocardial region subtended by the previously stenosed artery. The dipyridamole-induced increase in maximal myocardial blood flow is also impaired for ≥24 h after the procedure. The coronary vasodilator response in the angioplasty region is therefore impaired for ≥7 days after angioplasty. Thus, there is abnormal resistive vessel function in the coronary vascular bed distal to a coronary artery stenosis that persists for between 7 days and 3 months after the procedure.

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