

# A comparison of two methods to measure coronary flow reserve in the setting of coronary angioplasty: intracoronary blood flow velocity measurements with a Doppler catheter, and digital subtraction cineangiography

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*Intracoronary blood flow velocity measurements with a Doppler balloon catheter and the radiographic assessment of myocardial perfusion with contrast media, before and after the intracoronary administration of papaverine, have previously been used to investigate regional coronary flow reserve. In the present study we applied both techniques in 21 patients to measure coronary flow reserve in the setting of coronary angioplasty. Pre-angioplasty (N=14) and post-angioplasty (N=19) measurements of coronary flow reserve were obtained by digital subtraction cineangiography in the myocardial region supplied by the dilated coronary artery, and with the Doppler probe in the proximal part of the dilated vessel. The reactive hyperaemia following the final balloon inflation was recorded with the Doppler balloon catheter still positioned across the stenotic lesion. Coronary stenosis geometry was quantified with the Cardiovascular Angiography Analysis System. When the epicardial stenosis was the only factor causing a reduction in coronary flow reserve, flow reserve measured with both digital subtraction cineangiography and with the Doppler probe correlated well with the cross-sectional area at the site of obstruction,  $r=0.88$ ,  $SEE=0.36$  and  $r=0.77$ ,  $SEE=0.45$  respectively. In contrast, when other factors decreasing coronary flow reserve were present (intimal dissection, left ventricular hypertrophy, previous myocardial infarction, collaterals) measurements obtained with both techniques correlated poorly with cross-sectional area ( $r=0.55$ ,  $SEE=0.57$ , and  $r=0.59$ ,  $SEE=0.50$ ). Flow reserve measurements obtained with digital subtraction cineangiography correlated well with the measurements obtained with the Doppler probe ( $r=0.85$ ,  $SEE=0.38$ , and  $r=0.87$ ,  $SEE=0.34$ ), although the two approaches have methodologically nothing in common and their respective regions of interest (myocardium for the radiographic technique and intracoronary lumen for the Doppler technique) are basically different. Furthermore, the reactive hyperaemia following the final balloon inflation was related to the flow reserve measured with both the angiographic technique ( $r=0.85$ ,  $SEE=0.34$ ) and the Doppler technique ( $r=0.83$ ,  $SEE=0.32$ ) using pharmacologically induced coronary vasodilation with intracoronary papaverine. This suggests that the same quantity of coronary flow reserve that can be recruited pharmacologically can be recruited by ischaemia following a transluminal occlusion.*

## Introduction

Since the introduction of percutaneous transluminal coronary angioplasty (PTCA) in 1977<sup>[1]</sup>, the

procedure has gained increasing importance in the treatment of coronary artery obstructions. So far, the immediate results of the procedures have been assessed by coronary angiography and the residual pressure gradient. However, the change in luminal size of an artery following the mechanical disruption of its internal wall cannot be accurately assessed from the detected angiographic contours<sup>[2,3]</sup>. The measured residual pressure gradient may have short and long-term prognostic value, but it reflects only the haemodynamic state at rest<sup>[4-6]</sup>.

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Recently the assessment of coronary flow reserve has been proposed as a better method to evaluate the functional results of dilatation of a coronary artery obstruction<sup>[7-10]</sup>. Papaverine is currently regarded as the vasodilator of choice for the induction of maximal hyperaemia, as intracoronary administration results in an immediate, potent and short-lasting hyperaemia<sup>[11,12]</sup>. Intracoronary blood flow velocity measurements with a Doppler probe, and the radiographic assessment of myocardial perfusion with contrast media have previously been used to investigate regional coronary flow reserve<sup>[13-17]</sup>. In the present study we compared both techniques in the setting of PTCA, and compared the pharmacologically induced vasodilation after intracoronary papaverine with reactive hyperaemia following transluminal occlusion.

### Patients and methods

21 patients undergoing elective PTCA for angina pectoris were studied. All patients had evidence of myocardial ischaemia as indicated either by ECG changes at rest or by thallium scintigraphy during exercise. Informed consent was obtained for the additional investigations. All patients were studied without premedication, but their medical treatment (nitrates, calcium antagonists and beta-blockers) was continued on the day of the procedure.

#### PROTOCOL

1. Coronary cineangiography was performed in at least two, preferably orthogonal projections for quantitative analysis of the coronary artery stenosis, after intracoronary administration of 2 or 3 mg intracoronary isosorbide dinitrate. The intracoronary administration of isosorbide dinitrate was repeated at regular intervals (20–30 min) to ensure constant and maximal epicardial coronary vasodilation during the entire procedure<sup>[18]</sup>.

2. Coronary flow reserve was measured by digital subtraction cineangiography.

3. A long (315 cm) guide wire (diameter: 0.014 in) was passed through the coronary artery stenosis.

4. A balloon catheter with a Doppler probe at the tip<sup>[9]</sup> was advanced over the guide wire into the coronary artery to measure coronary blood flow velocity. The precise location of the tip of the balloon catheter with respect to the stenotic lesion — immediately proximal to the lesion and beyond any major side branches — was determined by injection of contrast medium. After recording the baseline intracoronary blood flow velocity,

hyperaemia was induced by injecting 12.5 mg papaverine through the guiding catheter. The ratio of peak mean intracoronary blood flow velocity to baseline was then determined as previously described by Wilson *et al.*<sup>[13]</sup> This measurement was obtained in 14 patients (Table 1).

5. Thereafter the balloon was advanced across the stenosis and three to seven inflations, lasting 40–80 s, and up to 12 atmospheres were used to dilate the stenosis until repeat cineangiography showed a good result (<50% diameter stenosis). The mean total inflation time was 162 s (patient<sup>-1</sup>) (range: 120–352 s). Immediately following the final balloon inflation the reactive hyperaemia was recorded. On average, four dilatations were performed per patient with sequential mean inflation times of 54, 60, 63, and 68 s. The inflation pressure increased on average for the four inflations from 7.6 to 10.4, 11.4 and 12.0 atmospheres. Reactive hyperaemia lasted 56 s (range 42–74 s). After each of the first three dilatations, both resting and hyperaemic velocities increased. On average, the velocities of the last two dilatations did not differ statistically, suggesting that the end result had been achieved by the third dilatation. However, some patients still had a substantial increase after the fourth dilatation and might well have benefited from additional dilatations.

The results of the sequential balloon inflations and the effects on coronary flow reserve have been previously described<sup>[9]</sup>.

6. After subsidence of this reactive hyperaemic response, the Doppler tip was pulled back into the proximal part of the coronary artery and the ratio of peak mean intracoronary blood flow velocity after 12.5 mg papaverine i.c. to baseline velocity was again determined. This measurement was obtained in 19 patients (Table 1).

7. After removal of the balloon catheter and the guide wire, coronary flow reserve was measured by digital subtraction cineangiography, at the same pacing rate and using the same radiographic and injection parameters as before PTCA.

8. Coronary cineangiography was repeated post-PTCA in the same projections as were used at the start of the procedure, for quantitative analysis of the coronary artery stenosis.

#### QUANTITATIVE ANALYSIS OF THE CORONARY ARTERY

The determination of coronary arterial dimensions from 35 mm cinefilm was performed with a computer-based Cardiovascular Angiography Analysis System (CAAS), described previously in

Table 1 Clinical characteristics and results

Patient	F/M	Age	No of DV	Vessel	B/A	OA	AS	DS	HR1	Ao1	CFR DSC	HR2	Ao2	CFR DOP	RH
1 (D)	F	48	1	LAD	A	5.4	35	19	70	91	2.0	67	104	2.1	2.2
2	M	43	1	LAD	A	4.8	51	30	70	95	3.3	51	92	2.9	2.9
3	M	58	1	RCA	A	2.9	64	40	70	93	2.8	68	98	3.0	2.8
4 (C)*	M	69	1	RCA	A	2.2	66	42	80	91	1.2	72	87	1.1	1.0
5	M	58	2	LAD	B	1.2	86	62	70	99	0.6	57	95	0.9	2.3
6	M	62	1	LAD	A	3.3	63	39	70	83	2.4	70	89	2.9	2.0
7 (D)	F	53	1	LAD	B	0.9	86	62	90	97	1.0	69	101	0.9	2.0
8	M	56	1	LAD	A	3.5	40	23	90	97	2.0	83	103	1.8	2.3
9 (I)*	M	53	1	LAD	B	1.6	72	47	90	82	2.0	71	80	1.8	2.3
10 (D)	M	55	1	LAD	A	3.5	51	30	90	78	2.4	81	76	2.7	2.2
11 (C)*, (D)	M	53	1	LAD	B	0.7	88	64	100	83	0.8	91	85	1.1	2.6
12 (H)*	F	57	1	LAD	A	3.7	24	17	100	88	2.2	85	98	2.3	1.7
13	M	66	2	LAD	B	1.2	83	59	80	90	1.1	70	90	1.3	2.1
14	M	56	1	CX	A	4.5	37	21	80	88	3.0	82	89	2.3	1.9
15	M	67	2	CX	A	2.5	49	28	80	96	1.7	70	97	1.9	2.6
16	M	60	1	RCA	B	2.7	69	45	70	85	2.2	60	79	2.0	1.7
17 (D)	M	56	1	LAD	B	2.9	59	35	70	115	1.1	66	112	1.0	2.1
18 (D)	M	37	1	LAD	A	5.3	41	23	70	111	1.7	62	108	2.2	2.1
19	M	49	1	RCA	B	0.7	82	58	70	81	1.4	59	83	1.2	1.9
20 (D)	F	76	1	LAD	A	2.9	44	25	70	84	2.7	61	83	2.4	1.5
21	M	58	1	LAD	B	0.7	87	63	70	81	1.2	61	83	1.1	1.5
				CX	B	0.9	86	68	70	88	1.3	58	88	1.0	1.5
				LAD	A	1.7	69	37	70	76	1.8	60	79	1.7	1.5
				LAD	B	1.3	78	53	80	93	1.4	73	89	1.6	1.6
				LAD	B	0.8	86	62	70	91	1.1	61	96	2.5	1.3
				RCA	A	2.7	61	37	70	92	1.0	57	99	1.4	1.0
				LAD	B	1.8	70	45	70	87	1.1	63	89	1.1	1.3
				RCA	A	1.4	84	60	80	95	1.3	73	99	1.4	1.0
				LAD	B	2.5	73	48	80	86	1.6	76	83	1.7	1.3
				LAD	A	1.1	75	50	80	91	1.3	63	90	1.4	1.5
				LAD	B	2.8	36	20	80	82	2.3	81	80	2.5	1.5
				LAD	A	0.6	90	69	70	80	1.0	65	82	1.2	1.6
				LAD	A	2.2	64	40	70	75	2.2	63	76	2.3	1.6

(\* = patients with conditions known to alter coronary flow reserve other than epicardial stenosis (C = collaterals, I = myocardial infarction, H = hypertrophy), D = dissection, F = female, M = male, No of DV = number of diseased vessels, LAD = left anterior descending coronary artery, RCA = right coronary artery, CX = circumflex artery, B = before PTCA, A = after PTCA, OA = cross-sectional area at the site of obstruction (mm<sup>2</sup>), AS = percentage area stenosis, DS = percentage diameter stenosis, HR = heart rate in beats min<sup>-1</sup> and Ao = mean aortic pressure (mmHg), 1 = immediately preceding CFR-DSC measurements, 2 = immediately preceding the CFR-DOP and RH measurements, CFR-DSC = coronary flow reserve measured with distal subtraction cineangiography, CFR-DOP = coronary flow reserve measured with Doppler.

detail<sup>[15,19,20]</sup>. In essence, boundaries of a selected coronary artery segment are detected automatically from optically magnified and video digitized regions of interest of a cineframe. The absolute diameter of the stenosis expressed in mm is determined using the guiding catheter as a scaling device. This involves automatic edge-detection of the boundaries of the catheter in situ and comparison of this value with the actual diameter measurement of the catheter using a micrometer. Calibration of the diameter in absolute values (mm) is achieved by comparing the mean diameter of the guiding catheter in pixels with the measured size in millimetres. Each catheter is measured individually<sup>[21]</sup>. To correct the detected contour of the arterial and catheter segments for pincushion distortion, a correction vector is computed for each pixel based on a computer-processed cineframe with a centimetre grid placed against the input screen of the image intensifier<sup>[20]</sup>. Since the functional significance of a stenosis is related to the expected normal cross-sectional area of the vessel at the point of obstruction, we use a computer estimation of the original arterial dimension at the site of the obstruction to define the interpolated reference area<sup>[19,20]</sup>. The percentage diameter and area stenosis and the minimal luminal diameter (mm) and cross-sectional area (mm<sup>2</sup>) are then calculated.

#### CORONARY FLOW RESERVE MEASUREMENTS WITH DIGITAL SUBTRACTION CINEANGIOGRAPHY

The coronary flow reserve measurement from 35 mm cinefilm has been implemented on the CAAS<sup>[15]</sup>. The heart was paced in the atrium at a rate just above the spontaneous heart rate. An ECG-triggered injection into the coronary artery was made with Iopamidol® at 37 °C through a Medrad Mark IV® infusion pump. This non-ionic contrast agent has a viscosity of 9.4 cP at 37°, an osmolarity of 0.796 osm.kg<sup>-1</sup> and an iodine content of 370 mg ml<sup>-1</sup>. The angiogram was repeated 30 s after a bolus injection of 12.5 mg papaverine into the coronary artery by way of the guiding catheter<sup>[11,12]</sup>. The injection rate of the contrast medium was judged to be adequate if back flow of contrast medium into the aorta occurred. When this was not observed on the hyperaemic image, baseline and hyperaemic image acquisition were repeated at a higher flow rate, necessitating flow rates of up to 6 ml s<sup>-1</sup> in some patients. Five or six consecutive end-diastolic cineframes were selected for analysis. Logarithmic non-magnified mask-mode background subtraction was applied to the image subset

to eliminate non-contrast medium densities<sup>[22]</sup>. The last end-diastolic frame prior to the administration of contrast was chosen as the mask. From the sequence of background subtracted images, a contrast arrival time image was determined using an empirically derived fixed density threshold<sup>[15]</sup>. Each pixel was labelled with the sequence number of the cardiac cycle numbered from the cycle in which pixel intensity first exceeded the threshold. In addition to the contrast arrival time image, a density image was computed, the intensity of each pixel being representative of the maximal local contrast medium accumulation. The coronary flow reserve was defined as the ratio of the regional flow computed from a hyperaemic image and the regional flow of the corresponding baseline image.

Regional flow values were quantitatively determined using the following videodensitometric principle: regional blood flow (Q) = regional vascular volume/transit time<sup>[15]</sup>. Regional vascular volume was assessed from logarithmic mask-mode subtraction images, using the Lambert Beer relationship. Coronary flow reserve was then calculated as:

$$CFR = \frac{Q_h}{Q_b} = \frac{D_h}{D_b} \cdot \frac{T_b}{T_h}$$

where D is the mean contrast density and T the mean appearance time at baseline (b) and hyperaemia (h). Mean contrast medium appearance time and density were computed within a user-defined region of interest, which was chosen so that the epicardial coronary arteries visible on the angiogram, the coronary sinus, and the great cardiac vein were all excluded from the analysis<sup>[15]</sup>. Reproducibility data are shown in Table 2. Normal values for coronary flow reserve measured with this technique have previously been established<sup>[10,15]</sup>. The coronary flow reserve of 12 angiographically normal coronary arteries was 5.0 ± 0.8. Therefore a flow reserve below 3.4 (2 SD below the mean) is taken to be abnormal.

#### INTRACORONARY BLOOD FLOW VELOCITY MEASUREMENTS

Instantaneous mean cross-sectional flow velocity was measured with a Doppler unit operating at 20 MHz using an ultrasonic crystal mounted on the tip of the angioplasty catheter. A balloon diameter size of 3.0 or 3.4 mm was used. The cross-sectional area at the tip, the site of the balloon and the shaft of the catheter was measured by means of a microcaliper. The cross-sectional areas at the three

Table 2 Reproducibility of the coronary flow reserve measurements

		1°	2°	Difference $\pm$ SD	r	SEE
DSC	N = 13	2.1 $\pm$ 1.2	2.1 $\pm$ 1.2	-0.02 $\pm$ 0.26	0.98	0.26
DOP	N = 15	1.6 $\pm$ 0.3	1.6 $\pm$ 0.3	+0.03 $\pm$ 0.18	0.88	0.19

1° = first determination (mean  $\pm$  SD), 2° = second determination (mean  $\pm$  SD), DSC = digital subtraction cineangiography, analysis of repeated image acquisition taken 5 min apart, without change in patient position, pacing rate, contrast injection parameters or X-ray gantry settings, DOP = repeated intracoronary Doppler blood flow velocity measurements 5 min apart without change in patient or Doppler catheter position.

different sites were respectively: 1.2 mm<sup>2</sup>, 0.65 mm<sup>2</sup> and 1.5 mm<sup>2</sup>. The Doppler crystal has a 1.0 mm diameter annulus with a 0.5 mm central hole. Two leads are soldered to the crystal and pass through the catheter between the original 0.5 mm lumen and a thin-walled tube which serves as a new 0.4 mm lumen. The leads exit near the proximal luer hub and are wired to a two-pin plug for connection to the pulsed Doppler instrument. The connector cable contains an integral toroidal isolation transformer which insulates the patient from the instrument and which also provides impedance matching for more efficient energy transfer. The new inner lumen extends from the luer hub through the crystal, providing a smooth unobstructed path for a guide wire. Blood flow velocity is detected by the zero cross method from the catheter tip transducer using a bidirectional range-gated 20 MHz pulsed Doppler velocimeter designed specially for this purpose (Baylor College of Medicine). The master oscillator frequency of 20 MHz is pulsed at a frequency of 62.5 KHz. Each pulse is approximately 1 ms in width and therefore contains 20 cycles of the master oscillator frequency. The parameters chosen (master oscillator frequency = 20 MHz and pulse repetition frequency = 62.5 KHz) allow velocities up to 100 cm s<sup>-1</sup> to be recorded at a distance of up to 1 cm from the catheter tip. The sampling window was individually adjusted to obtain the optimal signal which (usually) resulted in a sampling window of 1.8 mm (range 1.5–2.0). The output of the pulsed Doppler is frequency shift ( $\Delta f$ , KHz) which can be related to blood velocity by the Doppler equation:  $\Delta f = 2F (V/c) \cos a$ , where F is the ultrasonic frequency (20 MHz), V is the velocity within the sample volume, c is the speed of sound in blood (1.500 m s<sup>-1</sup>), and a is the angle between the velocity vector and the sound beam. Using an end-mounted crystal with the catheter parallel ( $\pm 20^\circ$ ) to the vessel axis,  $\cos a = 1 \pm 6\%$ ,

and the relation between the Doppler shift and velocity is approximately 3.75 cm s<sup>-1</sup> (KHz)<sup>-1</sup>[17]. Previous calibration experiments in canine femoral and coronary arteries have shown that the measured Doppler shift frequency is proportional to volume flow measured by time collection<sup>[13,24]</sup>. Recently, Sibley *et al.*[17] validated clinically and experimentally the ability of a similar catheter with an end-mounted piezo-electric crystal to provide accurate continuous on-line measurement of coronary blood flow velocity and vasodilator reserve. In our laboratory, we verified the accuracy of each velocity probe by correlating velocity recorded with the Doppler probe in a 9 F femoral sheath with the volume flow measured by a timed collection of blood from the side branch of the same sheath. Graduated flow rates (range: 12–165 ml min<sup>-1</sup>) and the corresponding velocities (range: 1.2–8.2 KHz) were obtained by incremental balloon inflation with the balloon positioned in the sheath. This simple model allows the assessment of the flow velocity relation at different levels. As previously demonstrated, this relation is linear with correlation coefficients generally  $\geq 0.95$ <sup>[13,17]</sup>. Reproducibility data are shown in Table 2.

#### STATISTICAL METHODS

Results are expressed as mean  $\pm$  SD unless stated otherwise. Least squares linear regression analyses were used to define the relationships between the various measurements.

#### Results

The clinical characteristics, results of the quantitative analysis of the coronary angiogram and the coronary flow reserve measurements are shown in Table 1. The mean age of the 21 patients was 57 years (range: 37–76 years); 17 were male. 18 patients had single vessel coronary artery disease and three

Table 3 Haemodynamic data

	Before PTCA		After PTCA		DOP-HR
	DSC-CFR	DOP-CFR	DSC-CFR	DOP-CFR	
HR	78 ± 10	67 ± 9	76 ± 9	69 ± 10	69 ± 10
Ao	90 ± 9	91 ± 9	88 ± 8	90 ± 10	90 ± 10

Heart rate (HR, beats min<sup>-1</sup>) and mean aortic pressure (Ao, mmHg) immediately preceding the coronary flow reserve measurements with digital subtraction cineangiography (DSC-CFR) and coronary flow reserve and reactive hyperaemia measurements with the Doppler catheter (DOP-CFR and DOP-RH).

patients two-vessel disease. The investigated and dilated coronary artery was the left anterior descending artery in 14, the circumflex artery in three and the right coronary artery in four patients. In none of the patients was a side branch involved at the site of the lesion. The mean left ventricular ejection fraction was 67% and ranged from 38 to 81%. Patient 9 had sustained a myocardial infarction in the anterior wall resulting in a large akinetic segment and an ejection fraction of 38%. None of the other patients had clinical evidence for a myocardial infarction and all had normal wall motion and an ejection fraction >55%. In two patients (patients 4 and 11) the coronary arteriogram showed grade III/IV collateral filling of the PTCA vessel<sup>[23]</sup>. Patient 12 had long-standing arterial hypertension with left ventricular hypertrophy. None of the other patients had electrocardiographic, echocardiographic or angiographic evidence of left ventricular hypertrophy. The mean number of balloon inflations was 4.3 per patient (range 3–7). The dilation was successful in all patients, and none of them had a CPK-rise after the procedure. Seven patients had a dissection of the dilated coronary artery segment after the procedure. Five dissections were small (patients 1, 7, 10, 11 and 20), two dissections were of moderate severity (patients 17, 18). None of the dissections had clinical repercussions. The haemodynamic data of the individual patients are shown in Table 1 and mean values (±SD) of the heart rate and aortic pressure are given in Table 3. The cross-sectional area at the site of obstruction was 1.1 ± 0.6 mm<sup>2</sup> before, and 3.2 ± 1.1 mm<sup>2</sup> after PTCA. Percentage diameter stenosis was 58 ± 9% before, and 32 ± 10% after PTCA. Percentage area stenosis was 82 ± 8% before, and 52 ± 14% after PTCA. The interpolated reference area was 6.6 ± 1.6 mm<sup>2</sup> and ranged from 3.9 to 9.8 mm<sup>2</sup>. During the measurements with the Doppler catheter just proximal to

the stenosis, the tip of the catheter (1.2 mm<sup>2</sup>) occupied 18 ± 5% (range 12 to 31%) of the cross-sectional area of the coronary artery. The reactive hyperaemia was measured with the balloon part of the Doppler catheter (0.65 mm<sup>2</sup>) across the stenosis. In this situation the catheter occupied 20 ± 5%, (range: 12–37%) of the luminal cross-sectional area at the site of the stenosis.

This implies that coronary flow reserve assessed with both techniques after PTCA was measured in the presence of an area stenosis of 52 ± 14%, whereas reactive hyperaemia was assessed in the presence of a residual area stenosis of 62 ± 16%. In 14 patients a coronary flow reserve measurement with the angiographic technique was also obtained in a myocardial region supplied by a coronary artery which was not dilated and which had no significant stenosis (<50% diameter stenosis). The mean coronary flow reserve of these vessels was 3.4 ± 0.8 before PTCA and 3.3 ± 0.9 after PTCA. The relationship between coronary flow reserve measured with digital subtraction cineangiography (CFR-DSC) and the cross-sectional area at the site of obstruction (OA) is shown in Fig. 1. Patients 4, 9, 11 and 12 had conditions associated with a reduced coronary flow reserve, in addition to the presence of a coronary stenosis, and patients 1, 7, 10, 11, 17, 18 and 20 had a dissection after PTCA. In these 10 patients only a weak relationship was found between these two parameters: CFR-DSC = 0.27 OA + 0.9, (r = 0.55, SEE = 0.57). In the other patients in whom the epicardial narrowing was the sole factor determining the coronary flow reserve, a good relationship was found between these two parameters: CFR-DSC = 0.51 OA + 0.7, (r = 0.88, SEE = 0.36).

The relationship between coronary flow reserve measured with Doppler (CFR-DOP) and the cross-sectional area at the site of obstruction (OA) is shown in Fig. 2. The resting Doppler-shift

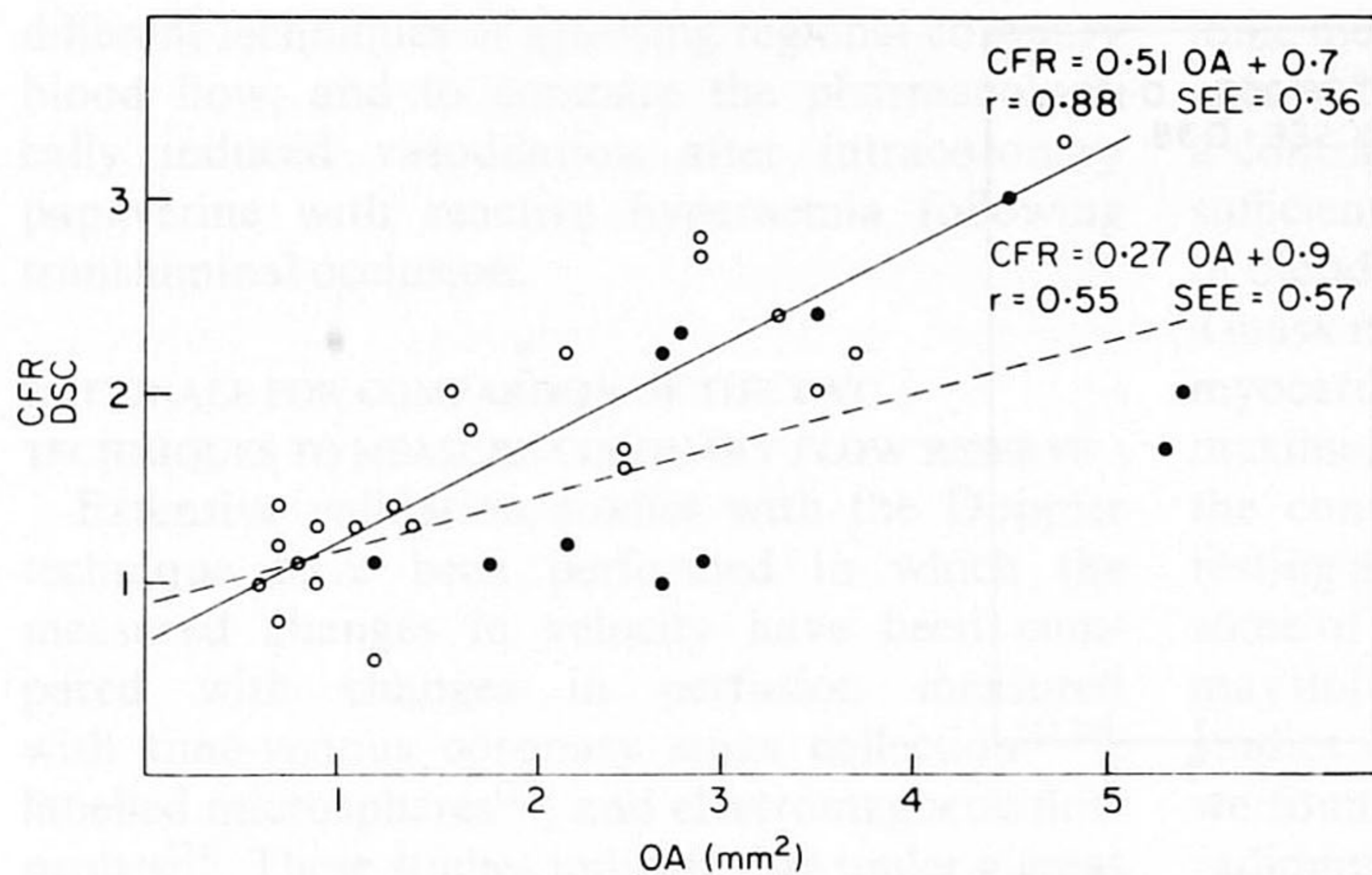


Figure 1 Relationship between coronary flow reserve measured with digital subtraction cineangiography (CFR-DSC) and cross-sectional area at the site of obstruction (OA). The open symbols are the patients with any of the following characteristics: left ventricular hypertrophy, hypertension, previous myocardial infarction, collaterals or dissection after PTCA. The closed symbols are the patients without any of the above listed characteristics.

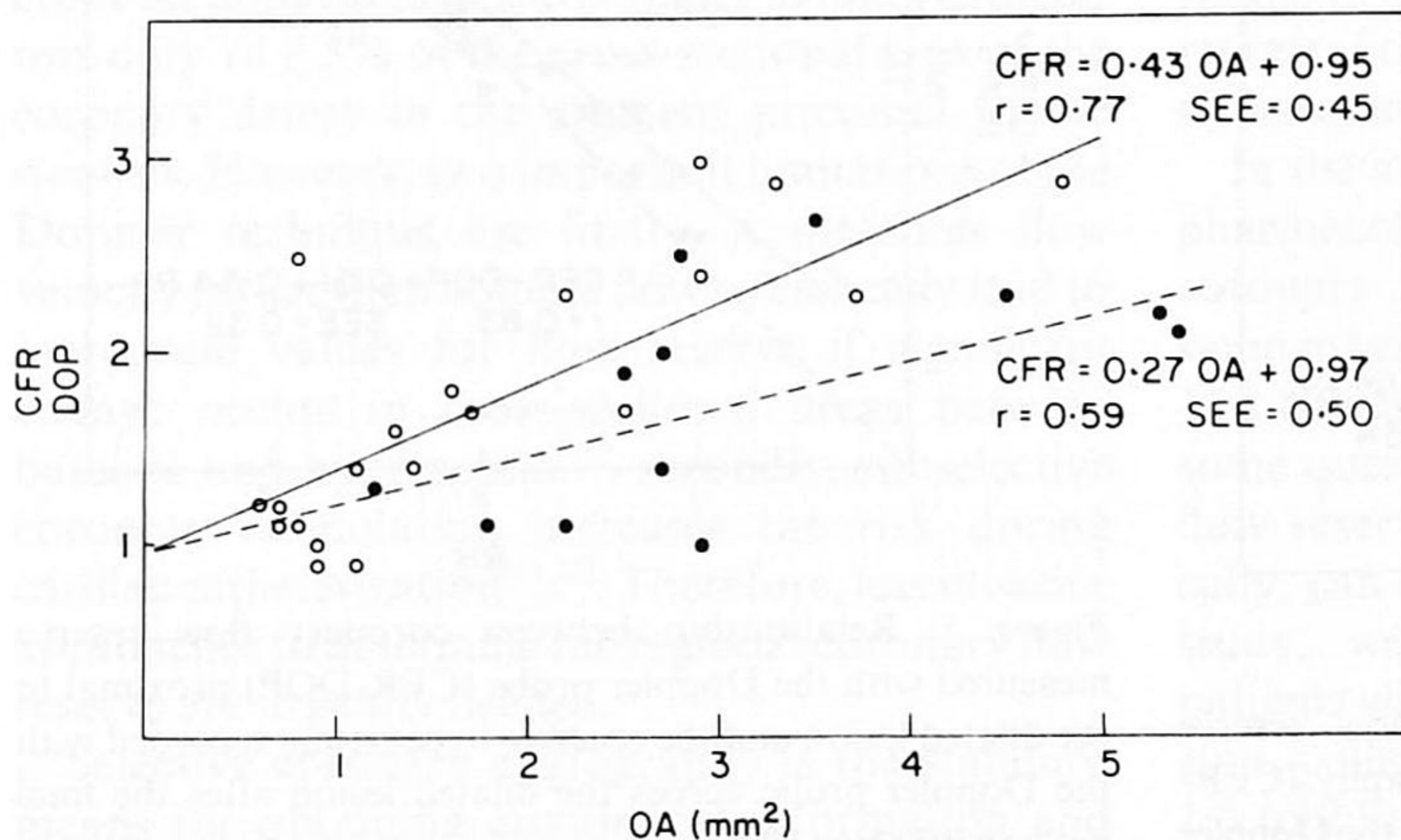


Figure 2 Relationship between coronary flow reserve measured with the Doppler probe (CFR-DOP) and cross-sectional area at the site of obstruction (OA). See Fig. 1 for explanation of symbols.

before PTCA was  $1.4 \pm 0.7$  KHz and after PTCA  $1.5 \pm 0.7$  KHz. In the patients with conditions associated with a reduced coronary flow reserve aside from the presence of a coronary stenosis the relationship between these two parameters was weak:  $\text{CFR-DOP} = 0.27 \text{ OA} + 1.0$  ( $r = 0.59$ ,  $\text{SEE} = 0.50$ ). In the other patients a reasonably good relationship was found between these two parameters:  $\text{CFR-DOP} = 0.43 \text{ OA} + 1.0$  ( $r = 0.77$ ,  $\text{SEE} = 0.45$ ).

The relationship between the coronary flow reserve measured with the angiographic technique and the coronary flow reserve measured with Doppler probe is shown in Fig. 3. There is a good relationship between the measurements made with these two techniques, irrespective of whether the flow reserve is limited solely by the severity of the coronary stenosis ( $\text{CFR-DSC} = 0.88 \text{ CFR-DOP} + 0.12$ ,  $r = 0.85$ ,  $\text{SEE} = 0.38$ ) or whether there are additional patient characteristics such as previous

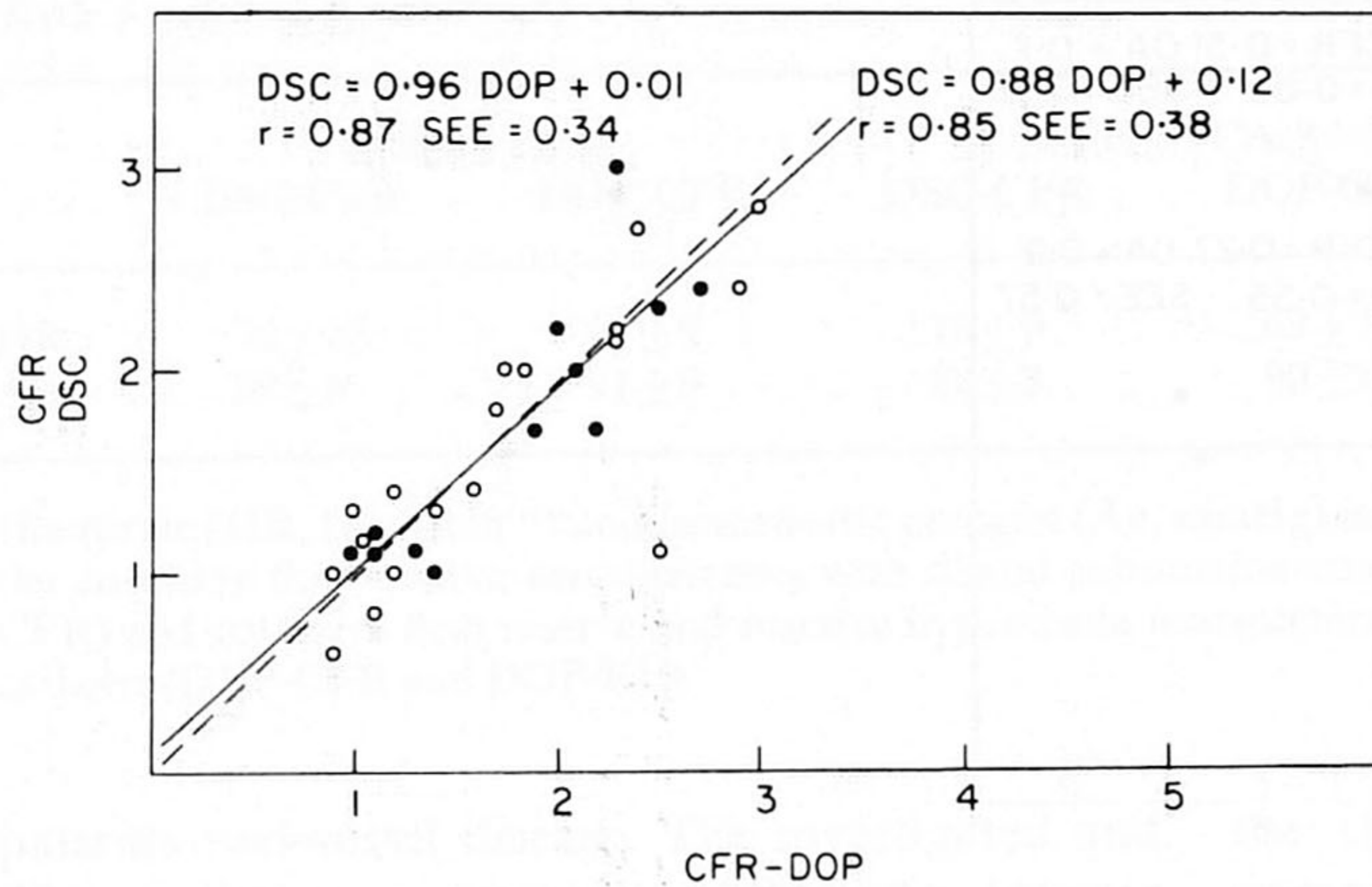


Figure 3 Relationship between coronary flow reserve measured with digital subtraction cineangiography (CFR-DSC) and coronary flow reserve measured with the Doppler probe (CFR-DOP). See Fig. 1 for explanation of symbols.

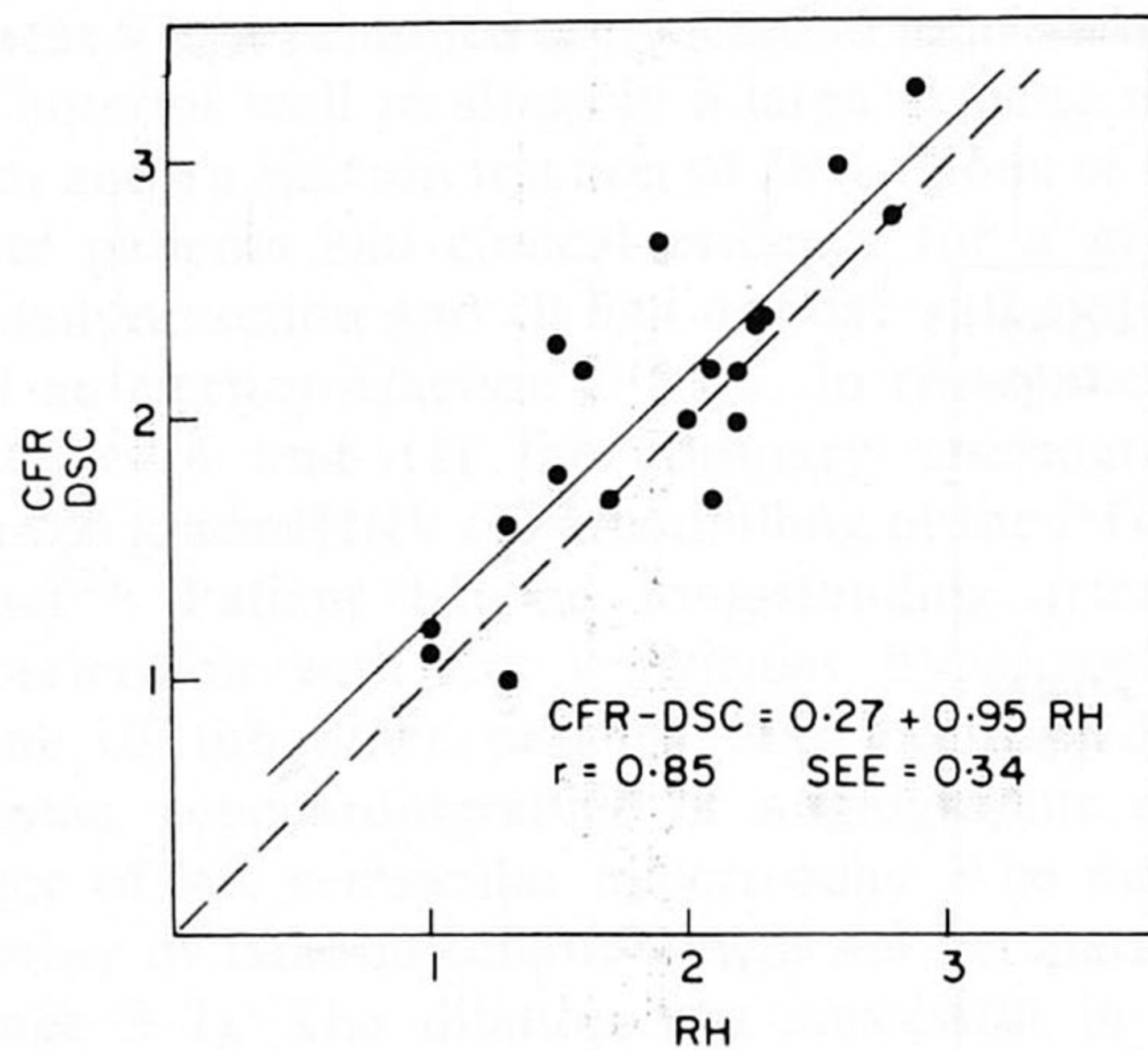


Figure 4 Relationship between coronary flow reserve measured with digital subtraction cineangiography (CFR-DSC) and the reactive hyperaemia recorded with the Doppler probe across the dilated lesion after the final balloon inflation (RH).

infarction, hypertrophy, collaterals or dissection after PTCA ( $\text{CFR-DSC} = 0.96 \text{ CFR-DOP} + 0.01$ ,  $r = 0.87$ ,  $\text{SEE} = 0.34$ ).

The relationships between the reactive hyperaemia (RH) recorded after the final balloon inflation with the angioplasty catheter still across the lesion, and coronary flow reserve measured with the angiographic technique ( $\text{CFR-DSC} = 0.27 + 0.95 \text{ RH}$ ,  $r = 0.85$ ,  $\text{SEE} = 0.34$ ) and with the Doppler catheter ( $\text{CFR-DOP} = 0.51 + 0.84 \text{ RH}$ ,  $r = 0.83$ ,  $\text{SEE} = 0.32$ ) are shown in Figs 4 and 5,

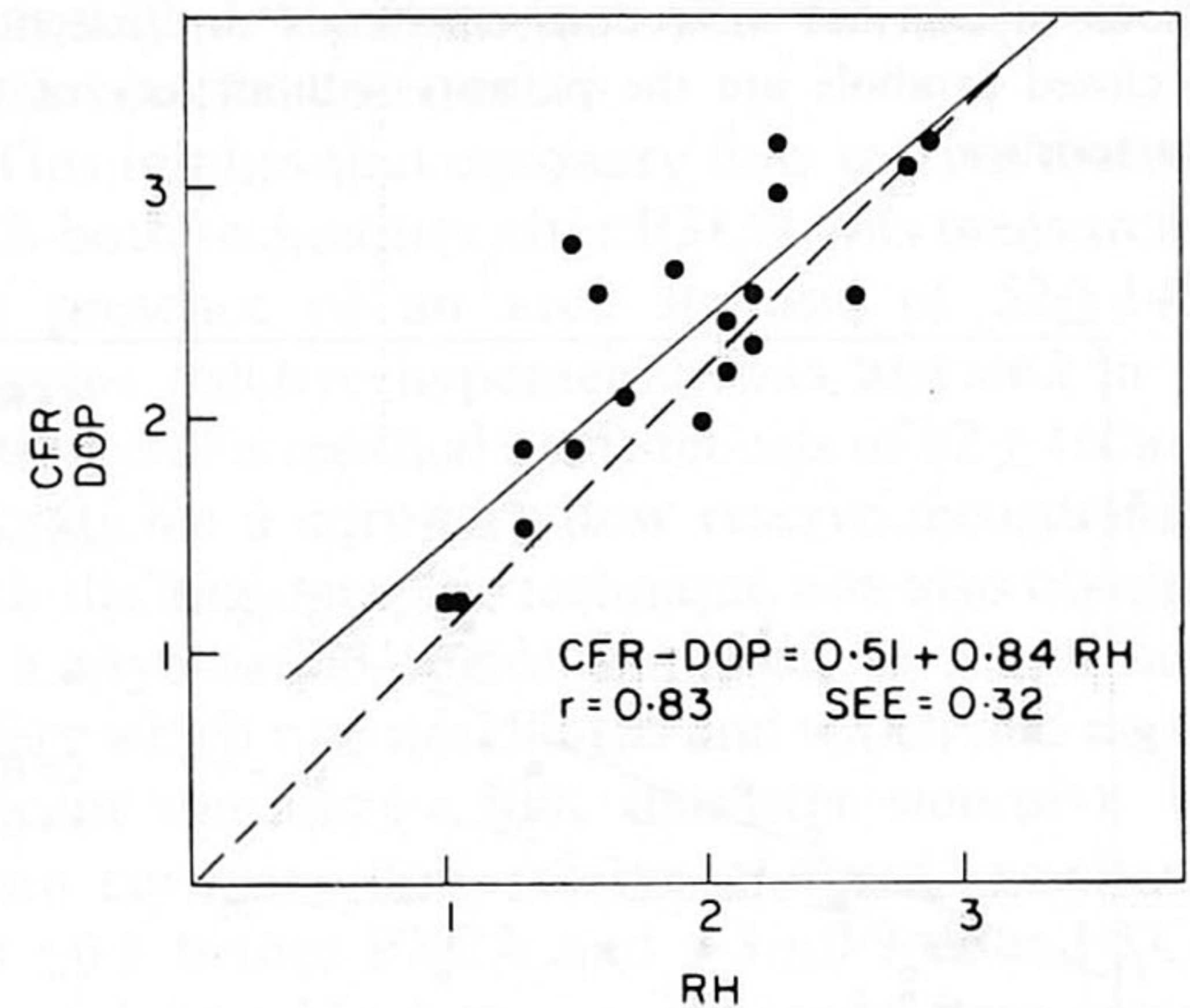


Figure 5 Relationship between coronary flow reserve measured with the Doppler probe (CFR-DOP) proximal to the dilated lesion and the reactive hyperaemia recorded with the Doppler probe across the dilated lesion after the final balloon inflation (RH).

respectively. As expected the mean reactive hyperaemia was somewhat lower than the coronary flow reserves measured with the angiographic technique or with the Doppler probe located proximal to the dilated stenosis. Reactive hyperaemia was  $1.9 \pm 0.6$ , coronary flow reserve measured with the angiographic technique  $2.1 \pm 0.6$  and coronary flow reserve measured with the Doppler catheter  $2.1 \pm 0.6$ .

## Discussion

The purpose of the present study was to compare in the setting of an angioplasty procedure two



different techniques of assessing regional coronary blood flow, and to compare the pharmacologically induced vasodilation after intracoronary papaverine with reactive hyperaemia following transluminal occlusion.

#### RATIONALE FOR COMPARISON OF THE TWO TECHNIQUES TO MEASURE CORONARY FLOW RESERVE

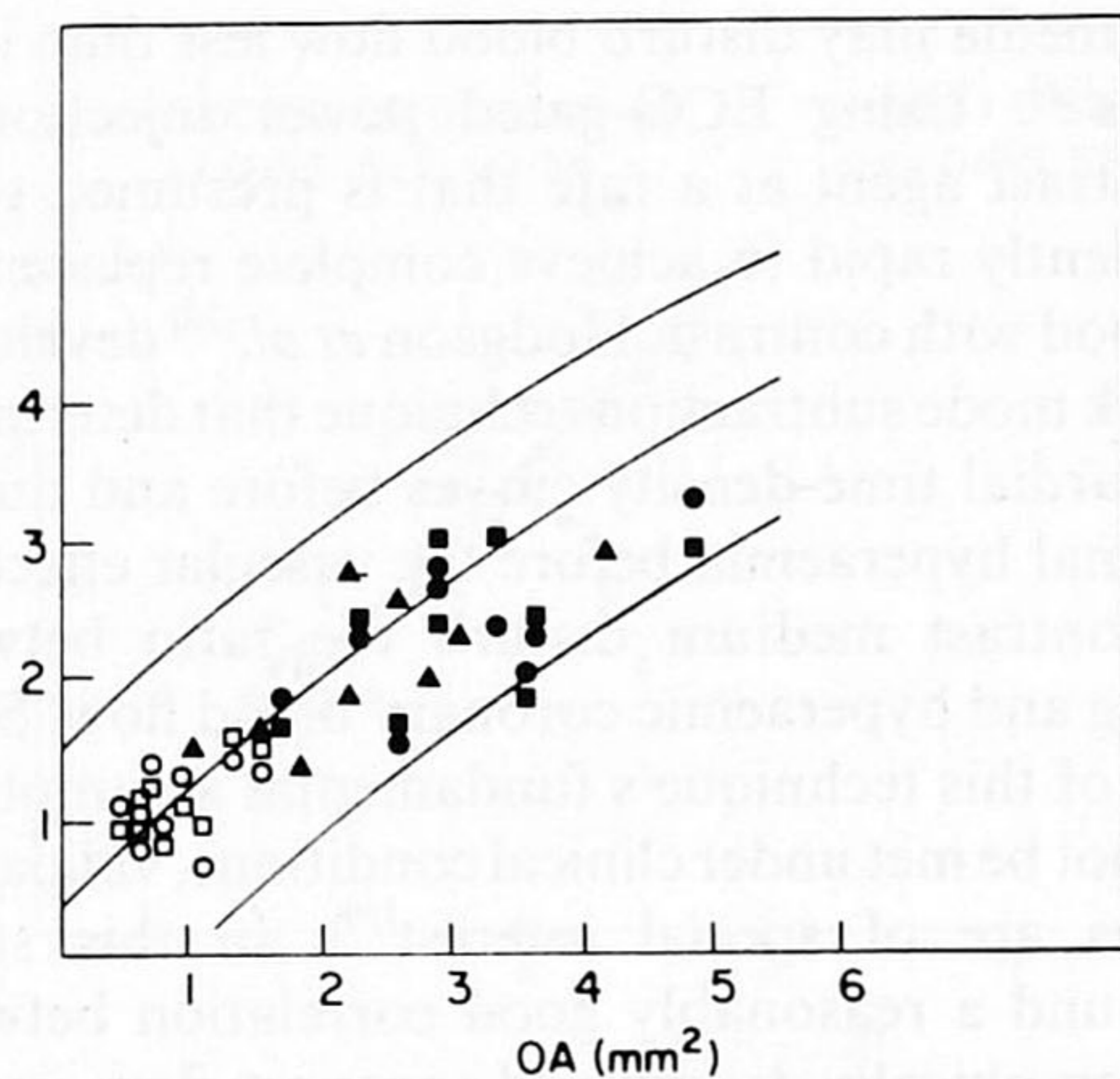
Extensive validation studies with the Doppler technique have been performed in which the measured changes in velocity have been compared with changes in perfusion measured with time-venous coronary sinus collection<sup>[13,24]</sup>, labelled microspheres<sup>[25]</sup>, and electromagnetic flow probes<sup>[24]</sup>. These studies indicate that under a great variety of conditions, changes in coronary blood flow velocity measured by the Doppler technique accurately reflect changes in flow<sup>[26]</sup>. Recently, small Doppler catheters have been developed and validated. They are able to make selective measurements of flow velocity in the major proximal coronary arteries<sup>[9,13,17]</sup>, without causing coronary obstruction<sup>[26]</sup>. For instance, in this report the cross-sectional area of the Doppler balloon catheter was only  $18 \pm 5\%$  of the cross-sectional area of the coronary artery in the segment proximal to the stenosis. However, two important limitations of the Doppler technique are firstly, it measures flow velocity rather than volume flow, which may lead to inaccurate values for flow reserve if significant change occurs in cross-sectional areas between baseline and hyperaemia<sup>[18]</sup>, secondly, subselective coronary cannulation increases the risk during cardiac catheterization<sup>[13,26]</sup>. Therefore, less invasive approaches to determine the regional coronary flow reserve are urgently needed.

Selective coronary angiography is the standard means for obtaining anatomical information and is the most important tool for clinical decision-making in patients with coronary artery disease. Recently, several attempts have been made to measure coronary blood flow parameters during cardiac catheterization using recent developments in radiographic technology<sup>[16]</sup>. However, radiographic contrast media cannot be used to measure coronary blood flow by the traditional methodologies<sup>[16]</sup>; an essential prerequisite of indicator dilution (Stewart-Hamilton), inert substance wash-out (Kety-Schmidt), and firstpass distribution (Sapirstein) techniques is that the indicator substance does not affect the regional flow being measured<sup>[8]</sup>. Unfortunately, all radiographic media have substantial vascular effects<sup>[27]</sup>, although non-

ionic media may disturb blood flow less than ionic agents<sup>[16]</sup>. Using ECG-gated power injection of a contrast agent at a rate that is presumed to be sufficiently rapid to achieve complete replacement of blood with contrast, Hodgson *et al.*<sup>[28]</sup> developed a mask mode subtraction technique that determines myocardial time-density curves before and during maximal hyperaemia before the vascular effects of the contrast medium disturb the ratio between resting and hyperaemic coronary blood flow. Since some of this technique's fundamental assumptions may not be met under clinical conditions, validation studies are of special interest<sup>[29]</sup>. In this study we found a reasonably good correlation between radiographically determined coronary flow reserve and the coronary flow velocity reserve measured with a Doppler probe, even though the two approaches have methodologically nothing in common and their respective regions of interest (myocardium for the radiographic technique and intracoronary lumen for the Doppler technique) are basically different.

#### MAXIMAL CORONARY BLOOD FLOW AFTER PHARMACOLOGICAL VASODILATION VS REACTIVE HYPERAEMIA INDUCED BY CORONARY OCCLUSION

In the animal laboratory it has been shown that pharmacologically induced vasodilation after intracoronary administration of papaverine is of the same magnitude as the reactive hyperaemia after a 15 s occlusion of the coronary artery<sup>[30]</sup>. There is some question as to whether the same quantity of flow reserve that can be recruited pharmacologically, can be recruited during ischaemia<sup>[29]</sup>. In this study, we found that reactive hyperaemia in patients without hypertrophy, infarction, hypertension, collaterals or dissection was  $2.1 \pm 0.6$  (range 1.3 to 2.9), whereas coronary flow reserve in these patients measured both with the Doppler probe and the radiographic technique was  $2.3 \pm 0.6$  (range 1.6–3.3) after PTCA. The cross-sectional area at the site of obstruction averaged  $3.05 \text{ mm}^2$  in these patients. Since the balloon catheter was still across the lesion the functional lumen averaged  $2.4 \text{ mm}^2$  (see Table 1). In a previous study from this laboratory we established the relationship between cross-sectional area at the site of obstruction and the measured coronary flow reserve in a patient population with single vessel coronary disease and the absence of other factors that might reduce flow reserve such as hypertrophy, infarction, hypertension, collaterals or dissection<sup>[15]</sup>. This relationship is shown in Fig. 6. A coronary artery with an obstruction area of



**Figure 6** Relationship between flow reserve and cross-sectional area at the site of obstruction (OA) as described in a previous report of our laboratory<sup>[15]</sup>. The lines indicate the best fit curve and the 95% confidence limits. The data of the present study are superimposed. The open symbols are the measurements obtained before PTCA. The closed symbols are the measurements obtained after PTCA. CFR-DSC (circles) = coronary flow reserve measured with digital subtraction cineangiography, CFR-DOP (squares) = coronary flow reserve measured with the Doppler probe, RH (triangles) = reactive hyperaemia recorded following the final balloon inflation.

2.4 mm<sup>2</sup> would be expected to have a vascular reserve of 2.2 with confidence limits extending from 1.3 to 3.0, which corresponds almost exactly to the range found in this study. Therefore, we feel that our data support the conclusion that the coronary vasodilation, after an optimal dose of intracoronary papaverine<sup>[11]</sup>, is equipotent to the reactive hyperaemia following a transluminal occlusion of more than 40 s in patients with significant coronary artery disease.

#### LIMITATIONS

When comparing these three measurements of the functional capacity of a coronary artery one has to bear in mind the potential sources of data scatter. Fortunately, the radiographic techniques as well as the Doppler technique have a good reproducibility (see Methods). Coronary flow reserve and reactive hyperaemia are both ratios of maximal coronary blood flow to resting flow. Resting coronary blood flow is mainly determined by aortic pressure and heart rate and coronary blood flow during maximal vasodilation is linearly related to the prevailing perfusion pressure<sup>[7,8]</sup>. These two haemodynamic parameters change little between the measurements of flow reserve and reactive hyperaemia (Tables 1

and 3), although they certainly contribute to the scatter of the data (Figs 3, 4 and 5).

Several studies have shown that in selected patients a close relationship exists between quantitatively determined stenosis geometry and measured coronary flow reserve<sup>[15,31]</sup>. However, coronary flow reserve can be influenced by many factors other than epicardial coronary stenosis, such as myocardial hypertrophy, tachycardia, hypertension, prior myocardial infarction, collaterals, dissection after PTCA<sup>[33]</sup>, changes in coronary vasomotor tone and changes in ventricular end-diastolic and intrathoracic pressures<sup>[7,8]</sup>. Therefore, in order to relate the measured coronary flow reserve to quantitatively determined stenosis geometry, we have carefully divided our study population into a group of patients (A) with one or more of the above mentioned characteristics and a group of patients (B) without any of these characteristics (Figs 1 and 2). We tried to prevent changes in vasomotor tone, which is relevant to both techniques<sup>[18]</sup>, by inducing a constant maximal epicardial coronary vasodilation with repeated intracoronary administration of isosorbide dinitrate<sup>[18]</sup>. In accordance with previous reports<sup>[15,31]</sup> we found a good correlation between cross-sectional area at the site of obstruction and measured coronary flow reserve in group B, in contrast to the poor correlation between these two parameters in group A.

#### CORONARY FLOW RESERVE IMMEDIATELY AFTER PTCA

Several authors<sup>[10,32]</sup> have shown that the coronary flow reserve of the myocardial region supplied by the dilated vessel increases substantially after PTCA, but is not restored to normal values. The measurements obtained in the present study with two independent techniques confirm this fact. We also measured the coronary flow reserve of an adjacent myocardial region supplied by a coronary artery not significantly diseased using the radiographic technique, and found a marked difference in vasodilator response. For ethical reasons we did not obtain this measurement with the Doppler catheter as we felt that introduction of the Doppler probe into a second coronary artery might introduce additional risk to the investigational part of the procedure. Nevertheless, the results of the radiographic technique indicate that the abnormal vasodilatory response is restricted to the myocardium supplied by the dilated coronary artery. There are several potential explanations for this phenomenon.

1. Since coronary flow reserve is the ratio of resting flow to maximal coronary blood flow, any increase in resting flow results in a decrease of this ratio. Neither of the techniques we used provided us with absolute measurements of volume flow. Therefore, we cannot make a definite conclusion regarding resting coronary volume flow after the PTCA. However, the resting Doppler shift was virtually the same before and after the PTCA procedure,  $1.4 \pm 0.7$  KHz and  $1.5 \pm 0.7$  KHz, respectively. Furthermore, several authors, using the thermodilution technique in the coronary sinus or the great cardiac vein, have reported comparable resting volume flows before and after PTCA<sup>[34-36]</sup>.

2. Metabolic, humoral or myogenic factors potentially play a role in the limited restoration of coronary flow reserve after PTCA. However, the metabolic derangements due to the PTCA seem quickly reversible<sup>[34,37,38]</sup>. Although humoral factors may play a role in a specific subgroup of patients with complicated PTCA, no evidence has yet been presented to implicate humoral factors in the majority of patients<sup>[39]</sup>. The chronic reduction in perfusion pressure distal to the stenotic lesion may induce alterations in the complex mechanism of autoregulation and a prolonged period may be needed before these abnormalities subside<sup>[40]</sup>.

3. Finally, the impaired coronary flow reserve might be directly related to the residual stenosis<sup>[10]</sup>. Cross-sectional area measured immediately after PTCA generally increases about threefold due to the procedure but remains grossly abnormal<sup>[10,41]</sup>. The relationship between cross-sectional area at the site of obstruction and coronary flow reserve as found in a previous study from our laboratory<sup>[15]</sup> is shown in Fig. 6 with the 95% confidence intervals. Data from the present study for patients fulfilling the same exclusion criteria (group B) are superimposed: coronary flow reserve measured with both techniques and the reactive hyperaemia following the final balloon inflation with residual obstruction area corrected for the presence of the Doppler balloon catheter. The large majority of measurements fall within the 95% confidence limits of this relation, suggesting that the persisting reduction in cross-sectional area per se is sufficient to explain the limited restoration of coronary flow reserve, although it does not exclude other contributing pathophysiological mechanisms.

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