Does the quantitative assessment of coronary artery dimensions predict the physiologic significance of a coronary stenosis?

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ABSTRACT To study the relationship between the quantitatively assessed coronary artery dimensions and the regional coronary flow reserve as measured by digital subtraction cineangiography, we investigated 17 coronary arteries with a single discrete proximal stenosis and 12 normal coronary arteries before and after intracoronary administration of papaverine. Coronary flow reserve was found to be curvilinearly related to minimal luminal cross-sectional area ($r = .92$, SEE = 0.73) and to percentage area stenosis ($r = .92$, SEE = 0.74). Normal coronary arteries had a coronary flow reserve of 5.0 (± 0.8 [SD]), which differed significantly from the coronary flow reserve of the coronary arteries with obstructive disease, in which values ranging from 0.5 to 3.9 were found. Coronary arteries with a percentage area stenosis between 50% and 70% and a minimal luminal cross-sectional area between 2 and 4.5 mm^2 differed significantly ($p = .001$), with respect to the coronary flow reserve, from coronary arteries with a percentage area stenosis in excess of 70% and a minimal luminal cross-sectional area less than 2 mm^2. With the use of hemodynamic equations that describe the pressure loss over a stenosis, a theoretical pressure-flow relationship can be inferred that characterizes the severity of the stenosis. Based on this theoretical pressure-flow relationship, coronary arteries that have a limited coronary flow reserve and critical stenosis (distal coronary perfusion pressure below 40 mm Hg at coronary flow of 3 ml/sec) can be identified with high sensitivity (83%) and specificity (82%). Thus, in coronary artery disease the consequent reduction in coronary flow reserve can be predicted with reasonable accuracy by quantitative assessment of coronary artery dimensions.
Circulation 75, No. 6, 1154–1161, 1987.

VISUAL INTERPRETATION of the coronary angiogram inadequately predicts the physiologic importance of obstructive coronary artery disease (CAD).[1] Computer-based quantitative analysis has helped minimize the problems of high interobserver and intraobserver variability in the assessment of the coronary angiogram,[2–4] and it allows the calculation of the pressure-flow characteristics of the coronary artery lesion[5] that are correlated with the translesional pressure gradient and with results of exercise thallium perfusion scintigraphy.[6, 7] However, the relationship between the quantitative analyzed dimensions of an obstructive coronary artery lesion and the consequent limitation in coronary blood flow is not yet fully understood. The recent description of a digital angiographic technique for the measurement of relative coronary blood flow has rendered the assessment of regional coronary flow reserve possible by use of the ratio of maximal coronary blood flow to resting flow as a measurement of this variable.[8] The goal of this investigation was to study the relationship of quantitatively assessed coronary artery dimensions and calculated coronary artery pressure-flow characteristics to the regional coronary flow reserve as measured by digital subtraction cineangiography.

Patients and methods

Seventeen coronary arteries of patients with single-vessel CAD and 12 coronary arteries of patients with normal coronary arteries were studied. The 17 coronary artery lesions were all single discrete stenoses in the proximal parts of the vessels before any significant sidebranch occurred. Coronary angiography by the Sones or Judkins technique was performed for chest pain syndromes. Informed consent was obtained for the

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Received May 14, 1986; revision accepted Jan. 22, 1987.

additional investigation. All patients were studied without premedication, but their medical treatment (nitrates, calcium antagonists, and β-blockers) was continued on the day of the investigation. None had systemic hypertension, cardiac hypertrophy, anemia, polycythemia, documented previous myocardial infarction, valvular heart disease, or angiographic evidence of collateral circulation.

The procedures for the determination of the coronary flow reserve and the quantitative assessment of coronary arterial dimensions from 35 mm cinefilm were implemented on the computer-based Cardiovascular Angiography Analysis System (CAAS), and have been extensively described.[4, 9]

Angiographic procedure and induction of a maximal hyperemic response. The heart was atrially paced at a rate just above the spontaneous heart rate. An electrocardiographically triggered injection into the coronary artery was made with iopamidol at 37° C through a Medrad Mark IV infusion pump. This nonionic contrast agent has a viscosity of 9.4 cp at 37° C, an osmolality of 0.796 osm·kg^{-1}, and an iodium content of 370 mg/ml. For the left coronary artery 7 ml was injected at a flow rate of 4 ml/sec; the coronary angiogram was obtained in a left anterior oblique projection. For the right coronary artery 5 ml was injected at a flow rate of 3 ml/sec and the angiogram was taken in a left or right anterior oblique projection. The rate of injection of the contrast medium was judged to be adequate when blackflow of contrast medium into the aorta occurred. The angiogram was repeated 30 sec after a bolus injection of 10 mg papaverine into the coronary artery.[10]

Quantitative coronary cineangiography. For the assessment of the absolute and relative dimensions of selected coronary segments with the CAAS, the boundaries of a selected coronary segment are detected automatically from optically magnified and video-digitized regions of interest (ROIs) of a cineframe. Calibration of the diameter data in absolute values (mm) is achieved by detection of the boundaries of a section of the contrast catheter and comparison of the computed mean diameter in pixels with the known size in millimeters. Each catheter is measured individually.[11] To correct the contour positions of the arterial and catheter segments for the pincushion distortion, a correction vector is computed for each pixel based on a computer-processed cineframe of a centimeter grid placed against the input screen of the image intensifier.[9]

The procedure for contour detection requires the user to indicate a number of center positions with the writing tablet proximal and distal to the lesion such that the straight-line segments connecting these points are within the artery. The contours of the vessel are detected on the basis of the weighted sum of first- and second-derivative functions applied to the digitized brightness information along scanlines perpendicular to the local centerline directions. From the detected contours the diameter function is determined in absolute millimeters. In this study, each lesion was analyzed in at least two, preferably orthogonal projections. Three projections were used if two orthogonal projections could not be obtained of a nonsymmetric lesion.

Since the functional significance of a stenosis is also related to the expected normal cross-sectional area of the vessel at the point of the obstruction, we use a computer estimation of the original arterial dimensions at the site of the obstruction to define the reference region (interpolated reference).[4, 9] Representative examples of two orthogonal views with the detected contours of a right coronary artery and the reconstructed reference contours are shown in figure 1. The computed reference diameter function allows for tapering of the vessel.

The interpolated percentage area stenosis (AS) is then computed by comparing the squared minimal diameter value at the obstruction with the squared value of the reference diameter function at this position, assuming a circular cross section:

$$AS = (1 - (\text{minimal diameter}/\text{reference diameter})^2) \times 100\%$$

The estimation of the length of the obstruction is made on the basis of a curvature analysis of the diameter function.[9] Coronary perfusion pressure distal to the stenosis is estimated by subtracting from the mean aortic pressure the theoretical pressure drop over the stenosis for coronary flows of 1, 2, and 3 ml/sec.[5, 12] The theoretical pressure drop was calculated according to the following hemodynamic equation:

$$PD = \frac{8\,\pi\,\mu\,L}{MLCA}\left(\frac{1}{MLCA}\right)Q + \frac{d}{0.266}\left(\frac{1}{MLCA} - \frac{1}{NA}\right)^2 Q^2$$

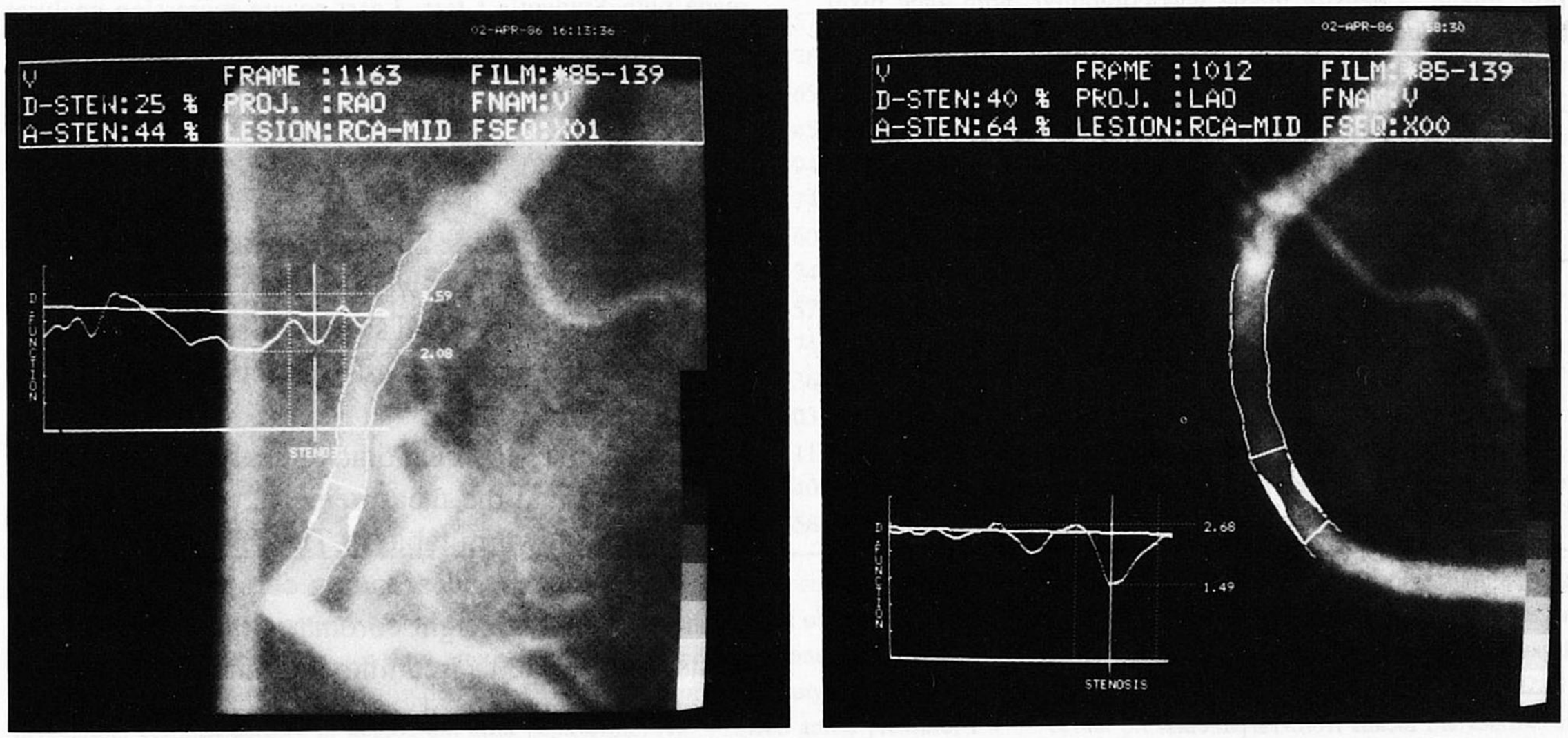

FIGURE 1. Detected contours from a representative stenosis in the right coronary artery superimposed on the original video image. The normal size of the artery over the obstruction is estimated by the interpolated method, and the resulting reference contours are shown. *A*, Right anterior oblique projection. *B*, Left anterior oblique projection.

where PD = pressure drop; μ = absolute blood viscosity; L = stenosis length; NA = interpolated normal cross-sectional area; MLCA = minimal luminal cross-sectional area; Q = volume flow; d = blood density.[13, 14] Since each stenosis was analyzed in two or 3 angiographic projections, two or three pressure drops were calculated and the mean value was used.

To assess the influence of 10 mg intracoronary papaverine on the dimensions of the epicardial coronary arteries, coronary angiograms obtained before and during the measurement of coronary flow reserve were compared. Nine normal coronary arteries and eight coronary arteries with a focal obstructive lesion were analyzed quantitatively. These eight coronary arterial segments were selected because the obstructive lesions were clearly visible and perpendicular to the image intensifier during the measurement of coronary flow reserve.

Coronary flow reserve measurements. For the quantitation of the relative coronary blood flow,[8] five to eight end-diastolic cineframes were selected from successive cardiac cycles. Logarithmic nonmagnified mask-mode background subtraction was applied to the image subset to eliminate noncontrast medium densities. The last end-diastolic frame before administration of contrast was chosen as the mask. Each digitized image was also corrected for the dark current of the video camera. From the sequence of background-subtracted images, a contrast arrival time image was determined with the use of a fixed-density threshold. In this image, each pixel was labeled with the sequence number of the cardiac cycle in which the pixel intensity level for the first time exceeded the threshold, starting from the beginning of the electrocardiographically triggered contrast injection. This density threshold was empirically derived by analyzing in 12 patients the relationship between the threshold and the baseline and hyperemic myocardial contrast medium appearance times as well as the resulting coronary flow reserve. The intensity level in more than 90% of pixels exceeded thresholds of 4%, 8%, and 12% (table 1). In 25% of patients less than 90% of pixels reached the intensity level of 16%, making calculation of the contrast medium accumulation unreliable. With a threshold of 4%, and to a lesser extent with a threshold of 8%, background noise was not eliminated, resulting in very short contrast medium appearance times. We therefore used a threshold of 12% in all our patients. In addition to the contrast arrival time image, a density image was computed, with each pixel intensity value being representative of the maximal local contrast medium accumulation. In the second step, the information from these two images was combined into a dual parameter image, the contrast medium appearance picture. In this picture the appearance time was color coded and the contrast medium accumulation was represented by the color intensity.

TABLE 1

Influence of density threshold on myocardial contrast medium appearance time and coronary flow reserve (CFR)

	DT (%)			
	4	8	12	16
AT1	1.96	2.48	2.88	3.39
AT2	1.58	1.73	1.97	2.19
CFR	2.26	2.63	2.66	2.82
	$p<.01$	NS	$p<.01$	

Values are means from 12 patients.

DT = density threshold in percentage of the brightness scale; AT1 = baseline myocardial contrast medium appearance time; AT2 = hyperemic myocardial contrast medium appearance time.

The coronary flow reserve was defined as the ratio of the regional flow computed from a hyperemic image divided by the regional flow of the corresponding baseline image. Regional flow values were quantitatively determined by use of the following videodensitometric principle: regional blood flow (Q) = regional vascular volume (RVV)/transit time. Regional vascular volume was assessed from the logarithmic mask-mode subtraction images. Since at the flow rates we used essentially all epicardial blood is replaced by contrast, the brightness information is proportional (factor k) to the local thickness of the projected vascular system, and thus:

$$RVV = k \int_R V(p)\, dp$$

where V(p) is the intensity distribution function of the subtraction image, R is the selected ROI, and p the pixel position (Beers-Lambert relationship).

If the same regions of interest are used for baseline and hyperemic conditions, the coronary flow reserve can be determined from the regional blood flow values Q_h and Q_b at the hyperemic and baseline states, respectively:

$$\frac{Q_h}{Q_b} = \frac{k \int_R V_h(p)/AT_h}{k \int_R V_b(p)/AT_b} = \frac{CH_h}{AT_h} \div \frac{CD_b}{AT_b}$$

where CD is the mean contrast density and AT is the mean appearance time.

Mean contrast medium appearance time and density were computed within user-defined ROIs. The ROIs were chosen in such a way that the epicardial arteries visible on the angiogram, including diagonal and septal branches, the aortic root, the coronary sinus, and the great cardiac vein were excluded from the analysis.

When coronary angiograms were repeated within 5 min, no significant differences were found in appearance time or contrast density. The mean difference between duplicate measurements of appearance time was 7%, with a standard deviation of 8%. The mean difference between duplicate measurements of contrast density was 6%, with a standard deviation of 5%.

Statistical methods. Comparisons between groups were made with Student's t test. Least square regression analyses were used to find the "best fit" relationship between coronary flow reserve and the quantitatively assessed coronary artery dimensions.

Results

The mean age of the 29 patients was 56 years (range 31 to 71); four patients were women and 25 men. All 17 patients with CAD had single-vessel disease and all 29 patients had a normal left ventricular ejection fraction (>55%).

The results of the quantitative analysis of the coronary arteries and the measurements of coronary flow reserve are shown in table 2. The investigated vessel was the left anterior descending coronary artery in 16 of the patients, the right coronary artery in seven patients, and the left circumflex coronary artery in six patients. An average of 2.2 angiographic projections was used for the quantitative morphologic analyses of the coronary angiogram. The mean cross-sectional area of the 12 normal coronary arteries, measured in

the proximal parts before any branching, was 7.6 mm^2 (range 5.4 to 10.3). The interpolated reference cross-sectional area of the vessels with CAD was 7.0 ± 1.7 mm^2. In vessels with CAD the area stenosis ranged from 51% to 93% (mean 76%), the minimal luminal cross-sectional area (MLCA) ranged from 0.4 to 4.1 mm^2 (mean 1.7), and the length of the obstructive lesions ranged from 3.0 to 13.6 mm (mean 7.0).

The influence of 10 mg intracoronary papaverine on the dimensions of normal coronary arteries and of coronary arteries with a focal obstructive lesion are shown in table 3. No change occurred in the cross-sectional areas of normal coronary arteries or those of the prestenotic and poststenotic coronary arterial segments after intracoronary papaverine. There was a small but significant decrease in area stenosis ($p < .05$, mean decrease 3%, ranging from 0 to 9%). The MLCA increased from a mean value of 2.1 to 2.6 mm^2 ($p < .05$, mean increase 24%, range 8% to 39%).

The 12 normal coronary arteries had a mean coronary flow reserve of 5.0 ± 0.8. Coronary flow reserve in vessels with coronary artery disease ranged from 0.5 to 3.9, with a mean of 1.6 ± 0.9, and differed significantly ($p < .001$) from that of normal coronary arteries. The relationship between coronary flow reserve and MLCA was best described by a quadratic equation:

$$CFR = 0.28 + 0.91\ MLCA - 0.039\ (MLCA)^2$$
$$(r = .92,\ SEE = 0.73)$$

TABLE 2
Results

			QACA[A]				CFR measurements					Ao	DPP (mm Hg)[A]					
	Vessel	Ang proj	MCLA (mm^2)	AS%	LL (mm)	NA (mm^2)	A1	D1	A2	D2	CFR	(mm Hg)	P1%	P1	P2%	P2	P3%	P3
1	LAD	LSO,RIO				7.6	2.7	77	1.1	202	6.5							
2	LCX	CA,CR				10.3	3.7	54	1.8	162	6.2							
3	LAD	CR,RIO				7.6	2.9	59	1.2	128	5.3							
4	RCA	RAO,LAO				7.3	3.3	69	1.5	163	5.2							
5	LCX	LAO,RIO				8.6	2.1	79	1.2	226	5.0							
6	LCX	RAO,LAO				5.7	3.7	57	1.5	115	5.0							
7	LAD	LSO/RIO				7.0	4.2	38	2.1	94	4.9							
8	RCA	RAO/LAO				7.8	3.3	42	2.2	133	4.8							
9	LAD	CR/CA				9.4	4.2	45	2.1	111	4.7							
10	RCA	RAO,LAO				9.8	3.6	70	1.8	161	4.6							
11	LAD	RAO,LSO				5.4	3.2	70	1.8	178	4.5							
12	LAD	CR,CA				4.7	2.2	80	1.2	148	3.4							
13	RCA	RAO,LAO	2.9	54	5.1	6.5	4.8	49	2.4	95	3.9	78	1	77	1	77	4	75
14	RCA	RAO,LAO	2.2	66	8.5	6.4	3.3	98	1.9	174	3.1	92	2	90	4	88	8	85
15	LAD	RAO,CR,CA	4.1	57	5.7	9.5	3.5	57	2.5	102	2.5	96	0	96	1	95	1	95
16	LCX	RAO,LAO	3.5	63	5.7	9.4	3.2	76	2.1	123	2.5	94	0	94	1	93	2	92
17	RCA	RAO,LAO	2.8	63	5.5	7.7	3.0	65	1.6	85	2.4	89	1	88	2	87	3	86
18	LCX	LAO,RIO,CA	3.2	51	3.0	6.5	2.9	45	2.1	54	1.7	84	0	84	1	83	2	82
19	LAD	LSO,CR,RIO	1.6	81	5.2	8.3	2.3	94	1.9	116	1.5	74	3	72	9	67	18	61
20	LAD	CR,CA	0.7	90	8.7	6.8	2.0	74	2.1	105	1.4	101	20	81	50	50	94	6
21	LAD	RAO,LSO,CR	0.9	82	13.6	5.1	2.8	60	2.6	73	1.3	86	19	70	44	48	77	20
22	LAD	CR,RIO,LSO	1.6	82	7.9	8.9	2.2	74	2.3	100	1.3	84	4	81	11	75	19	68
23	LAD	LAO,RIO	1.1	87	9.6	8.2	2.8	57	2.6	59	1.1	94	9	86	22	73	41	55
24	LAD	CR,CA,RAO	0.8	89	5.9	7.4	2.4	74	2.1	62	1.0	84	14	72	39	51	75	21
25	LAD	LSO,RAO	0.4	93	6.1	6.1	3.6	36	3.8	33	0.9	82	60	33	170	−58	332	−190
26	RCA	RAO,LAO	0.7	91	6.2	7.2	2.8	103	2.5	80	0.9	89	18	73	49	45	96	4
27	LAD	LSO,RAO	1.7	76	9.9	7.1	2.5	111	2.3	78	0.8	88	3	85	9	80	17	73
28	LCX	LAO,CA	0.7	89	5.1	6.1	1.4	40	2.3	47	0.7	79	18	65	51	39	97	2
29	LAD	CR,LSO,RIO	0.4	86	6.6	2.9	2.8	56	3.8	39	0.5	94	52	45	140	−38	267	−157

LAD = left anterior descending; LCX = left circumflex; RCA = right coronary; QACA = quantitative analysis of the coronary angiogram; Ang proj = angiographic projection; AS = area stenosis; LL = length of the obstructive lesions; NA = normal area from normal coronary arteries or interpolated reference area of coronary arteries with CAD; CFR = coronary flow reserve; A1 = myocardial contrast appearance time of basal angiogram; D1 = myocardial contrast density of basal angiogram; A2 = myocardial contrast appearance time of angiogram after papaverine; D2 = myocardial contrast density of angiogram after papaverine; Ao = mean aortic pressure; P% = actual pressure drop/Ao × 100%; DPP = distal coronary perfusion pressure at coronary flows of 1 ml/sec (P1), 2 ml/sec (P2) and 3 ml/sec (P3); LSO = left superior oblique; RIO = right inferior oblique; CR = cranial; RAO = right anterior oblique; LAO = left anterior oblique; CA = caudal.

[A]All values are mean values calculated from two or three angiographic projections.

TABLE 3
Influence of 10 mg intracoronary papaverine on coronary artery dimensions

Areas (mm^2) of the nine normal coronary arteries	Eight coronary arteries with focal obstructive coronary artery segments			
	Prestenotic area (mm^2)	MLCA (mm^2)	AS%	Poststenotic area (mm^2)
Before ic papaverine				
10.2	9.1	2.1	75	6.6
NS	NS	$p<.05$	$p<.05$	NS
Thirty seconds after ic papervine				
10.2	9.6	2.6	72	6.6

and is shown in figure 2. The relationship between coronary flow reserve and area stenosis was best described by a quadratic equation:

$$CFR = 5.0 - 3.3\,(AS \times 10^{-2}) - 1.3\,(AS \times 10^{-2})^2$$
$$(r = .92,\ SEE = 0.74)$$

and is shown in figure 3.

The 12 normal coronary arteries (group A) were compared with the six coronary arteries with a MLCA between 2 and 4.5 mm^2 and an area stenosis between 50% and 70% (group B) and with the 11 coronary arteries with a MLCA less than 2 mm^2 and an appearance time in excess of 70% (group C). In group C, coronary flow reserve was 1.0 ± 0.3 and differed significantly ($p = .001$) from that of group B (2.6 ± 0.7). The difference between group A and group B was also significant ($p < .001$; table 4).

From the MLCA, the length of the obstructive lesion, and the normal cross-sectional area distal to the stenosis a theoretical pressure-flow relationship was calculated for each angiographic projection from which the mean values were used for further analyses (table 2). The pressure-flow relationship for group B arteries differed significantly ($p < .01$) from that for group C. Group C could be subdivided with respect to coronary flow reserve on the basis of these theoretical pressure-flow relationships. The pressure-flow relationship of coronary arteries with a coronary flow reserve of 1 or less differed significantly from those of coronary arteries with a flow reserve greater than 1 ($p < .01$). A distal coronary perfusion pressure below 40 mm Hg at a coronary flow of 3 ml/sec identified five of six patients with a coronary flow reserve of 1 or less (sensitivity 83%). Only two of 12 vessels with CAD and a coronary flow reserve greater than 1 had a distal coronary perfusion pressure below 40 mm Hg (specificity 82%).

Discussion

In the clinical setting assessment of the relationship between the angiographic degree of stenosis and the actual impairment of perfusion has been hampered by two basic problems that now seem to have been solved by new technical developments. First, the recent description of a technique using digital subtraction angiography has rendered the assessment of regional coronary flow reserve possible during cardiac catheterization.[8] Second, the large intraobserver and interobserver variability associated with the visual assessment of the coronary angiogram has led to development of methods of computer-based quantitative analysis, including automated contour detection, which improve accuracy and allow for the precise determination of most dimensions of a given stenosis in a coronary artery.[4, 9]

Pharmacologic vasodilation. One of the methodologic cornerstones in the assessment of coronary flow reserve is the induction of a maximal hyperemic response.[15] A wide range of values for the coronary flow reserve of normal coronary arteries has been reported,

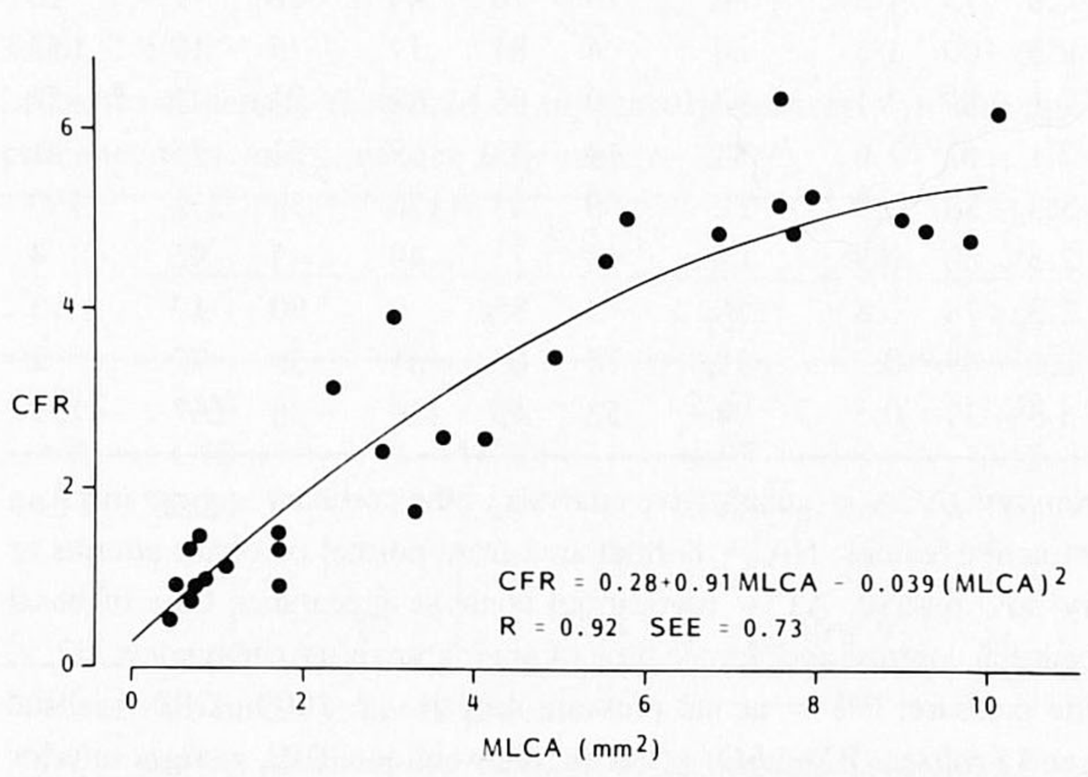

FIGURE 2. Relationship between coronary flow reserve (CFR) and MLCA.

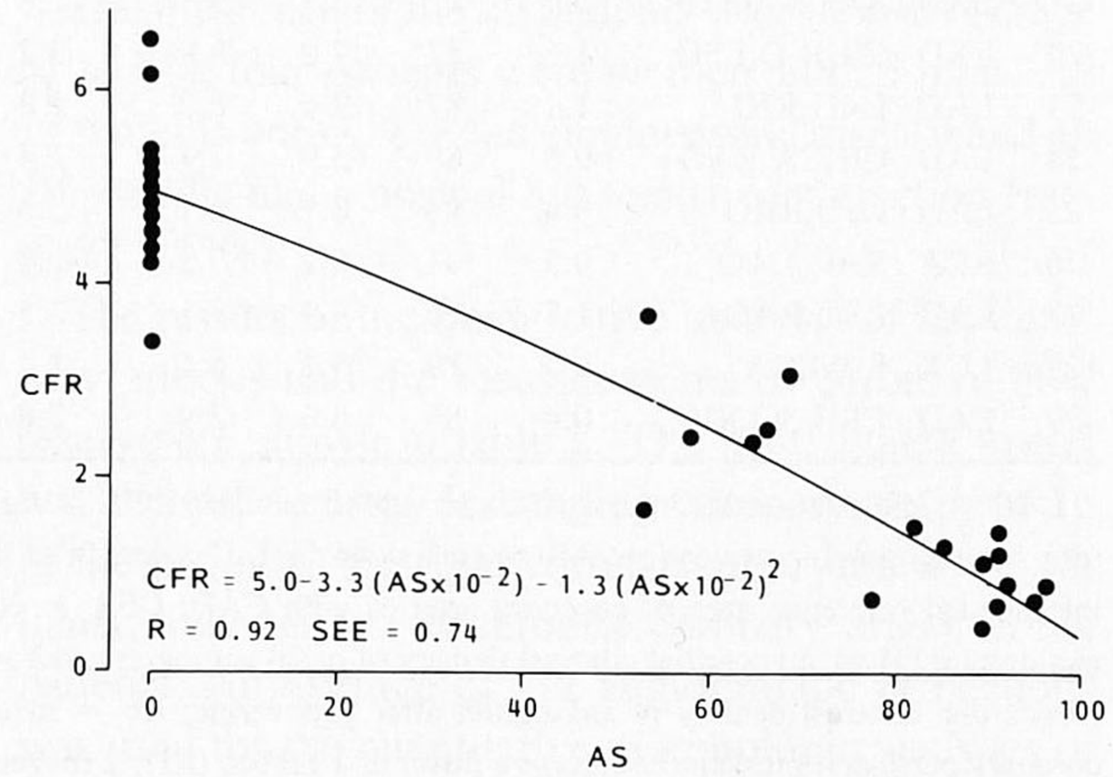

FIGURE 3. Relationship between coronary flow reserve (CFR) and percentage area stenosis (AS).

depending on the vasodilator used.[16, 17] Carefully validated studies with a Doppler-catheter suggest that the maximal coronary blood flow velocity of a normal coronary artery is four to six times the resting value.[16] The most commonly used vasodilator agents are dipyridamole and hyperosmolar ionic contrast media. An adequate intravenous infusion of dipyridamole results in maximal coronary vasodilation, but its long-lasting effect makes repeated assessment of the hyperemic response of a coronary vascular bed or assessment of different coronary vascular beds during the same procedure impossible. Hyperosmolar ionic contrast media do not produce maximal vasodilation.[10]

The exact dose of intracoronary papaverine that is needed to induce maximal coronary vasodilation has recently been established. Wilson and White[10] compared the coronary hyperemic response after 4, 8, 12, and 16 mg intracoronary papaverine and reported a maximal hyperemic response after 8 or 12 mg in all coronary arteries. Conversely, a coronary steal phenomenon has been observed after pharmacologic vasodilation. We recorded a coronary flow reserve of less than 1.0 in some of our patients who received papaverine, and Bates et al.[17] made the same observation in patients receiving hyperosmolar ionic contrast medium.

Relationship between coronary artery dimensions and coronary flow reserve. In the experimental animal the physiologic significance of artificially produced arterial stenoses has been extensively studied.[14, 18–21] Gould et al.[20] produced varying degrees of coronary narrowing and showed that stenoses in excess of 30% to 45% diameter narrowing reduced coronary vasodilator responses in a predictable fashion. However, in human beings with CAD the relationship between the visually estimated percentage diameter stenosis and the consequent reduction in coronary flow reserve is poor.[1] Harrison et al.[22] found that MLCA predicted the coronary flow reserve better than area stenosis in proximal lesions of the left anterior descending coronary artery. Due to diffuse CAD the estimation of the normal coronary arterial dimensions was impossible, and precluded the use of relative measures of severity of stenosis. In our patients the interpolated reference cross-sectional area of the vessels with CAD was on average 7.0 mm^2 and the cross-sectional areas of the 12 normal coronary arteries was on average 7.6 mm^2, which indicates the isolated and focal character of their CAD. Therefore, severity of stenosis could be assessed with absolute measurements (MLCA) as well as relative percentage (area stenosis) and these two variables were similarly related to CFR. Area stenosis and MLCA were curvilinearly related to coronary flow reserve and these relations were best described by quadratic equations. Harrison et al. found, in vessels with an expected normal cross-sectional area between 7 and 10 mm^2, that a MLCA below 3.5 mm^2 was predictive of a decreased coronary flow reserve. We observed, in vessels with an expected normal cross-sectional area of 7.0 ± 1.7 mm^2, that an MLCA below 4.5 mm^2 was associated with a decreased coronary flow reserve.

In a previous study from our laboratory the relationship between the pressure drop over a stenosis and the MLCA was analyzed.[7] A curvilinear relationship was found, with a steep increase in pressure drop once the MLCA is less than 2 mm^2. The present study confirms the discriminant value of this criterion (table 4).

Other angiographic factors that are important in the prediction of coronary flow reserve. A pressure-flow relationship that characterizes the severity of the coronary stenosis can be derived by means of hemodynamic equations using MLCA, the length of the obstructive lesion, and the normal cross-sectional area of the coronary artery. From the relationship between coronary perfusion pressure and coronary flow under conditions of maximal coronary vasodilation as described by Bache and Schwartz,[23] and assuming a resting coronary flow velocity of 15 cm/sec, Kirkeeide et al.[21] calculated a coronary flow reserve from the angiographic data. They showed in dogs the good correlation between such an angiographic approach and measured coronary flow reserve. In our patients the calculated pressure-flow relationships were related to the reduction in coronary flow reserve (table 5). A pressure drop over a stenosis at a flow of 3 ml/sec resulting in a distal perfusion pressure below 40 mm Hg indicated the existence of a critical stenosis, defined as a vessel with a coronary flow reserve of 1 or less. With the use of this criterion, patients with severe CAD and a critical stenosis could be identified with a

TABLE 4
Relationship between quantitatively assessed coronary artery dimensions and CFR

	Normal arteries (group A; n = 12)	Arteries with CAD	
		Group B (n = 6)	Group C (n = 11)
MLCA (mm^2)	>4.5	2–4.5	<2
AS (%)	0	50–70	>70
Mean ± SD CFR	5.0±0.8	2.6±0.7	1.0±0.3
		p<.001	p = .001

CFR = coronary flow reserve; AS = area stenosis.

TABLE 5
Calculated distal coronary perfusion pressure (mm Hg) for theoretical coronary flows of 1 (P_1), 2 (P_2), and 3 (P_3) ml/sec of vessels with CAD subdivided according to CFR

No. of patients		CFR		AS (%)	MLCA (mm^2)	Ao (mm Hg)	P1	P2	P3
		Mean	Range						
6	CFR>1.6	2.6	1.7–3.9	59	3.1	89	88	87	86
5	1<CFR<1.6	1.3	1.1–1.5	86	1.1	88	78	63	42
6	CFR≤1	0.8	0.5–1.0	87	0.8	86	62	20	−41

CFR = coronary flow reserve; AS% = mean percentage area stenosis; Ao = mean aortic pressure.

high sensitivity (83%) and specificity (82%) (table 6). The rationale for use of this pressure is based on previous observations that reactive coronary hyperemia is abolished when coronary artery perfusion pressure drops below this value.[24]

Limitations. The intracoronary administration of contrast medium results in profound alterations in coronary blood flow, characterized by depression in the first seconds followed by hyperemia.[25] The magnitude and timing of these changes depend primarily on amount, iodine concentration, and injection rate of the contrast medium.[26] The hyperemic-to-baseline coronary blood flow ratio nevertheless remains unchanged within the first 5 sec after the injection of contrast medium when care is taken to keep these factors constant.[25, 26] The selection of the fixed-density threshold influences the measured myocardial contrast medium appearance time, and thus the resulting coronary flow reserve. When, however, this threshold is chosen so that background noise is eliminated and more than 90% of pixels in the chosen ROI reach the threshold, this influence is insignificant (table 1).

Although we found a clear relationship between area stenosis, MLCA, and coronary flow reserve, individual coronary arteries with moderate CAD may differ considerably in coronary flow reserve. Approaches that integrate all angiographic dimensions are conceptually attractive,[21] but limited by the fact that coronary flow is estimated. We used theoretical flows of 1, 2, and 3 ml/sec to define the pressure-flow relationship since resting coronary blood flow in the left anterior descending artery is 1.3 (range 1.0 to 2.1) ml/sec.[6]

Many other factors are potential causes of a decreased coronary flow reserve. In addition to cardiac hypertrophy and previous myocardial infarction, anemia, polycythemia, valvular heart disease, and collateral circulation may influence coronary flow reserve.[27–30] We have carefully tried to exclude patients with these conditions.

Changes in vasomotor tone are not only an important source of variability in the analysis of the coronary angiogram,[4] but may also influence the measurement of coronary flow reserve.[30, 31] Therefore, we continued medical treatment, including nitrates and calcium antagonists, in all our patients with CAD on the day of the investigation. Most important to our study, this could affect measurement of the papaverine-induced change in geometry of stenosis. The increase in MLCA (mean 24%, range 8% to 39%) and the decrease in area stenosis (mean 3%, range 0 to 9%) are methodologically disturbing, since they result in an increase in the measured coronary flow reserve and contribute to the variability in the relationship between area stenosis, MLCA, and coronary flow reserve. Alterations in the volume of the epicardial coronary artery could also influence the measurement of coronary flow reserve by changing the coronary blood flow velocity and thus myocardial appearance time of the contrast medium. However, intracoronary papaverine did not change the diameter of normal coronary arteries nor the diameter of prestenotic and poststenotic coronary artery segments. This is contrary to the findings of others,[31] and probably a consequence of the medical treatment. Finally, these findings cannot be extrapolated to other patient subsets, for instance patients with more diffuse CAD, collateral circulation, or stenosis in more distal coronary arteries of smaller size.

In conclusion, the development of a digital angiographic technique to measure regional coronary flow

TABLE 6
Identification of coronary arteries with a critical stenosis on the basis of calculated distal coronary perfusion pressure (DPP)

DPP (mm Hg)	Mean ± SD CFR		CFR≤1 (n)	CFR>1 (n)
<40	0.96±0.3	]	5	2
		p = .01		
>40	2.1±0.9	]	1	9

Sensitivity: 5/6 × 100% = 83%; specificity; 9/11 × 100% = 82%.
CFR = coronary flow reserve.

reserve and computer-based quantitative analysis of the coronary angiogram, including automated contour detection, has made the assessment of the relationship between a coronary artery stenosis and its physiologic consequences possible in human beings during cardiac catheterization.

The reduction in coronary flow reserve as a result of a coronary artery stenosis can be predicted with reasonable accuracy by quantitative assessment of coronary artery dimensions.

We thank Gusta Koster and Anja van Huuksloot for their secretarial assistance in the preparation of this manuscript.

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