Quantitative angiography of the left anterior descending coronary artery: correlations with pressure gradient and results of exercise thallium scintigraphy

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ABSTRACT To evaluate, during cardiac catheterization, what constitutes a physiologically significant obstruction to blood flow in the human coronary system, computer-based quantitative analysis of coronary angiograms was performed on the angiograms of 31 patients with isolated disease of the proximal left anterior descending coronary artery. The angiographic severity of stenosis was compared with the transstenotic pressure gradient measured with the dilatation catheter during angioplasty and with the results of exercise thallium scintigraphy. A curvilinear relationship was found between the pressure gradient across the stenosis (normalized for the mean aortic pressure) and the residual minimal area of obstruction (after subtracting the area of the angioplasty catheter). This relationship was best fitted by the equation: normalized mean pressure gradient = a + b·log [obstruction area], r = .74. The measurements of the percent area of stenosis (cutoff 80%) and of the transstenotic pressure gradient (cutoff 0.30) obtained at rest correctly predicted the occurrence of thallium perfusion defects induced by exercise in 83% of the patients.
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IT IS UNCLEAR what degree of narrowing of a major epicardial coronary artery will consistently lead to myocardial ischemia during exercise.[1] Under experimental conditions, a 50% reduction in the luminal diameter can diminish the vasodilative reserve of the coronary vascular bed, but the resting blood flow is unaffected until the diameter stenosis exceeds 80% to 90%.[2] Moreover, an estimation of the severity of a stenosis based on the minimal cross-sectional area of the vessel is a more accurate descriptor of its hemodynamic impact than percent diameter narrowing, which is the traditional method for grading coronary stenoses.[3, 4] Furthermore, previous investigators have demonstrated the value of quantitative coronary angiography in assessing the physiologic significance of a coronary artery stenosis.[5–8]

In the clinical setting more precise assessment of the relationship between the arteriographic degree of stenosis and the actual impairment of perfusion is hampered by several limitations, the major one being the large intraobserver and interobserver variability in interpretation of coronary angiograms.[9, 10] Other limitations include inconstant vasomotor tone,[11, 12] the frequently irregular luminal geometry, and the extent to which collaterals are present.

To study the relationship between the stenotic diameter of a coronary artery and the pressure gradient across its stenosis on the one hand and the extent of myocardial ischemia induced by exercise on the other, we selected patients with single-vessel disease of the left anterior descending coronary artery for this study. In these patients angiograms were obtained after intracoronary injection of nifedipine. The severity of the residual stenosis was measured by a computerized

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quantitative analysis procedure, while exercise-induced ischemia was assessed by means of stress thallium scintigraphy.

Methods

Patients selection. Thirty-one consecutive patients with stable exertional angina pectoris were studied; all were candidates for percutaneous transluminal angioplasty of an isolated proximal left anterior descending stenosis. All subjects gave informed consent and no complications resulted from the study. Details regarding the procedure used in our laboratory have been previously described.[13, 14]

Quantitative coronary angiography. The quantitative analysis of selected coronary segments was carried out with the help of a computer-based Coronary Angiography Analysis System (CAAS) that is described in another report in this issue of the journal, as well as extensively elsewhere.[15–19] In short, the boundaries of a selected coronary segment were detected automatically from optically magnified and video digitized portions of a cine frame. Calibration of the diameter data from the vessels in absolute values (mm) was achieved by detecting the boundaries of a section of the contrast catheter and comparing the computed mean diameter in pixels with the known size in millimeters. Strictly speaking, this calibration factor is only applicable for coronary segments in the plane of the analyzed catheter segment parallel to the image intensifier input screen. The change in magnification for two objects located at different points along the x-ray beam axis is about 1.5% for each centimeter that separates the objects axially with the commonly used focus-image intensifier distances. In the present study the axial distance between catheter and stenosis was short so that the possible changes in the calibration factor were negligible and no further corrections were used. To correct the contour positions of the arterial and catheter segments for the pincushion distortion, a correction vector was computed for each pixel based on a computer-processed cine frame of a centimeter grid placed against the input screen of the image intensifier.[16]

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 first centerline position was selected beyond the take off of large daughter branches. The contours of the vessel were detected on the basis of the weighted sum of first and second derivative functions applied to the digitized brightness information with use of minimal-cost criteria.

From the detected contours the diameter function, in absolute millimeters, was determined. From the minimal value of the diameter function determined by the computer and the mean diameter value at the reference position, the percentage area (% A) stenosis, assuming circular cross sections, was computed as

$$\% \text{ A stenosis} = [1 - (\text{minimal diameter}/\text{reference diameter})^2] \times 100$$

A representative example of an image with the detected contours and the diameter function superimposed on the original video frame is shown in figure 1, *A*.

In arteries with focal obstructive lesions and clearly normal proximal arterial segments, the choice of the reference region is straightforward and simple. However, in cases in which the proximal or distal part of the arterial segment shows combinations of stenotic and ectatic areas, the choice may be very difficult. Since the functional significance of a stenosis is related to the expected normal cross-sectional area of the vessel at the point of the obstruction, we used two methods to define the reference region: one is dependent on the user (user-defined reference), while the other technique is based on the computer estimation of the original arterial dimensions at the site of the obstruction (interpolated reference).[18, 19] For the latter method, the computed reference diameter function allows for tapering of the vessel. An example of the resulting reference contours is shown in figure 1, *B*. The interpolated percentage diameter stenosis is then computed by comparing the minimal diameter value at the obstruction with the corresponding value of the

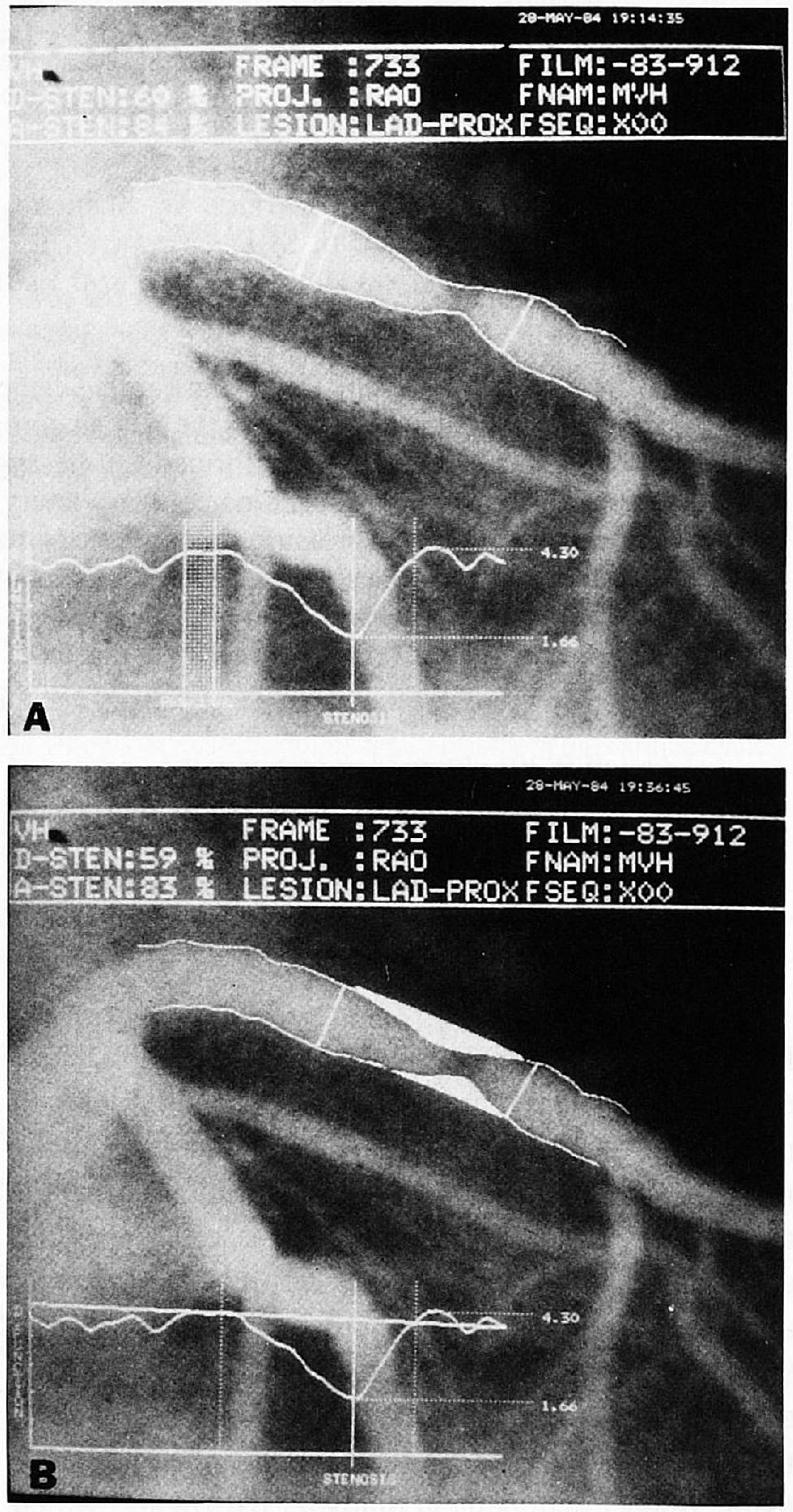

FIGURE 1. Detected contours for a representative stenosis of the left anterior descending coronary artery superimposed on the original video image. The diameter function is shown on the bottom. *A*, The reference diameter (or area) selected was proximal to the stenosis. The calibrated diameter values (in mm) are plotted along the ordinate starting from the proximal to the distal part of the analyzed segment along the abscissa. A percent area stenosis of 84% results. *B*, The normal size of the artery over the obstruction has been estimated by the interpolated method. The resulting reference contours are shown and the difference in area between this boundary and the detected contours is a measure of the amount of atherosclerotic plaque (shaded area). A percent area of stenosis of 83% results.

reference diameter function at this position. As described earlier, the percentage area stenosis can be calculated as well.

The validation of the techniques used has been described extensively in the companion report.[19]

In this study coronary angiograms were obtained within 5 min after intracoronary injection of nifedipine (0.1 to 0.2 mg) to obtain vasodilatation of the epicardial vessels and the relief of any possible spasm.[20, 21] Since the luminal cross section at the site of the coronary obstruction is frequently irregular in shape, especially after angioplasty,[22, 23] the average obstruction area and percent area obtained from multiple views were used (mean of 1.7 views per segment). Since the presence of the dilatation catheter within the stenotic lumen further reduces luminal area, the difference between the area measured from the coronary angiograms and the area of the balloon catheter (0.64 mm^2) was considered the actual residual lumen and related to the pressure gradient measurements. The mean pressure gradient across the stenotic lesion was measured with the dilatation catheter (mean diameter of 0.9 mm, Schneider 20–30 or 20–37) before and after angioplasty and calculated on-line after a data acquisition period of 20 sec.[24]

Noninvasive testing. Exercise thallium-201 myocardial scintigraphy was performed before angioplasty in seven patients, after angioplasty in 13 patients, and before and after the procedure in 11 patients. Sequential imaging was performed according to a standard protocol immediately after a symptom-limited exercise test and again 4 hr later. Scintigraphy was performed during the week before angiography (n = 18) and in the 3 weeks after successful angioplasty (n = 24). No patient had a recurrence of angina pectoris during this time interval. During exercise three orthogonal leads (X, Y, and Z) were monitored and analyzed as previously described.[25] The scintigraphic images were processed on a DEC gamma-11 system.[26] Basically, circumferential profiles were computed in three projections (anterior, 45 degree left anterior oblique, and 65 degree left anterior oblique) within the automatically detected contour of the left ventricle after background subtraction according to Watson et al.[27] The circumferential profiles, the processed images, and the analog Polaroid images were interpreted by three independent observers who were unaware of the angiographic data. The myocardial uptake of thallium was scored in 13 segments both for early and late exercise scintigrams in the following manner: 0 = no thallium uptake; 1 = severely abnormal; 2 = definitely abnormal; 3 = doubtfully abnormal; 4 = normal. These scores were summed per patient and the difference between late and early postexercise sums was taken as a measure of the amount of redistribution. By this approach, ischemia was considered to be present if at least two observers found that the redistribution score was 2 or more points higher than the early postexercise score. Since only patients with single-vessel disease were included, stenosis of the left anterior descending artery was assumed to be responsible for the regional defects observed in the anteroseptal, anterior, and anterolateral as well as apical segment.[28]

Statistical analysis. Simple regressions were used to find the best-fit relationship between the pressure gradient and the obstruction area. The Student t test for paired data and linear least squares regressions were used to compare the interpolated and user-defined percent area of stenosis. One-way analysis of variance followed by multiple comparisons was used to compare the angiographic measurements among three subgroups of patients. Data are expressed as mean ± SD.

Results

The absolute dimensions of the minimal obstruction area are listed in table 1 and are ranked from the mini-

TABLE 1
Results of quantitative angiography and exercise testing[A]

Patient No.	Time of test	Obstr area	Inter A st.	User A st.	$\Delta P/\overline{AoP}$	AP	ECG	^{201}Tl
1	b	0.15	98	96	0.75	–	–	+
2	b	0.30	98	94	0.49	+	+	–
3	b	0.36	97	97	0.87	+	+	+
4	b	0.45	96	84	0.46	+	+	+
5	b	0.58	96	94	0.54	–	–	+
6	b	0.58	92	91	0.55	–	–	–
7	b	0.65	93	90	0.74	–	+	+
8	b	0.80	90	(—)	0.38	–	BB	–
9	b	0.88	89	89	0.63	–	+	+
10	b	0.92	90	75	0.73	+	–	+
11	b	0.98	80	85	0.67	–	–	+
12	a	1.23	70	75	0.29	–	–	–
13	a	1.58	72	55	0.16	–	+	–
14	b	1.65	89	84	0.43	–	+	+
15	b	1.74	91	89	0.65	+	+	+
16	b	1.77	89	(—)	0.60	+	–	+
17	b	2.06	88	90	0.39	+	BB	+
18	b	2.09	88	87	0.72	–	+	+
19	b	2.38	62	69	0.39	–	BB	+
20	a	2.75	75	72	0.10	+	BB	–
21	a	2.83	38	65	0.13	–	–	–
22	a	2.95	34	50	0.18	+	–	–
23	a	3.00	55	65	0.10	–	–	–
24	a	3.11	54	64	0.13	–	+	–
25	a	3.14	60	(—)	0.09	–	–	–
26	a	3.14	44	32	0.06	–	–	–
27	a	3.17	66	65	0.28	–	–	–
28	b	3.33	65	65	0.15	–	–	+
29	a	3.70	56	54	0.34	–	–	+
30	a	3.94	61	30	0.16	–	–	–
31	a	4.12	48	39	0.11	–	–	–
32	a	4.16	66	48	0.16	–	+	–
33	a	4.26	37	45	0.21	–	+	–
34	a	4.34	65	56	0.04	–	–	–
35	a	4.95	37	52	0.00	–	–	–
36	a	5.68	44	43	0.16	–	–	–
37	a	6.20	62	67	0.18	–	–	–
38	a	7.07	64	53	0.21	–	–	+
39	a	7.50	60	57	0.10	–	–	–
40	a	8.29	6	14	0.21	–	+	–
41	a	9.90	30	21	0.07	–	–	–
42	a	17.87	6	6	0.06	–	–	–

b = before PTCA; a = after PTCA; Obstr. area = area of obstruction (in mm^2); A st. = percent area stenosis; inter = interpolated reference region; user = user-defined reference region; (–) = missing data; $\Delta P/\overline{AoP}$ = mean pressure gradient normalized for mean aortic pressure; AP = angina pectoris; ECG = ST depression ≧0.1 mV; ^{201}Tl = redistribution from exercise to rest scintigram; + = present; – = absent; BB = bundle branch block.

[A]See National Auxiliary Publication Service document No. 04255 for 2 pages of supplementary material. Order from NAPS c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163. Remit in advance in U.S. funds only $7.75 for photocopies or $4.00 for microfiche. Outside the U.S. and Canada add postage of $4.50 for the first 20 pages and $1.00 for each additional page; $1.50 for microfiche postage.

mal obstruction of 0.15 mm^2 to the maximal value of 17.9 mm^2. The interpolated and user-defined percent areas stenosis are shown as well. The user-defined reference region was proximal to the stenosis in all but 10 patients in whom it was distal because of the take-off of the left circumflex artery just before the stenosis. There was no significant difference between the interpolated and user-defined percent area stenosis: the difference between paired data was 1.7 ± 10 and the correlation coefficient was .91 (interpolated percent area of stenosis = 0.95 user-defined area + 4.8; SEE = 10). When the mean pressure gradient across the stenosis normalized for the mean aortic pressure was compared with the residual obstruction area after subtracting the balloon area (figure 2), a nonlinear relationship was found that can be described by the equation

$$\Delta P/\overline{AoP} = a + b \cdot \log \text{[obstruction area]}$$

where a = 0.35 and b = −0.12 (r = .74). There is a steep increase in pressure gradient once a critical value of 2.5 mm^2 of the stenotic segment is reached. In seven cases, the catheter used for angioplasty almost totally obstructed the vessel. The computed reduction in cross-sectional area is also related to the pressure gradient (figure 3). Here, the steep increase in pressure gradient is observed once a critical reduction of 80% of cross-sectional area is reached.

During the exercise test, the maximal workload averaged 85 ± 17% of the predicted value. According to the results of thallium scintigraphy, three types of responses are observed. In group I patients (n = 25), scintigrams were normal, with either a normal or abnormal exercise electrocardiogram. In group II patients (n = 7), thallium scintigrams were abnormal while exercise test results were normal. In group III patients (n = 10), both thallium scintigrams and exercise test results (angina and/or ST segment changes) were abnormal. The percent area stenosis was 55 ± 23% in group I, 74 ± 17% in group II, and 90 ± 4% in group III. The mean pressure gradient was 0.18 ± 0.13 in group I, 0.44 ± 0.23 in group II, and 0.62 ± 0.15 in group III. The pressure gradient measurements discriminated better between the groups than the area stenosis measurements (table 2). When both parameters were used, two groups of data points were delineated, as shown in figure 3. With use of cutoff values of 0.30 for the pressure gradient and 80% for the reduction in cross-sectional area, the results of exercise thallium scintigraphy were correctly predicted from

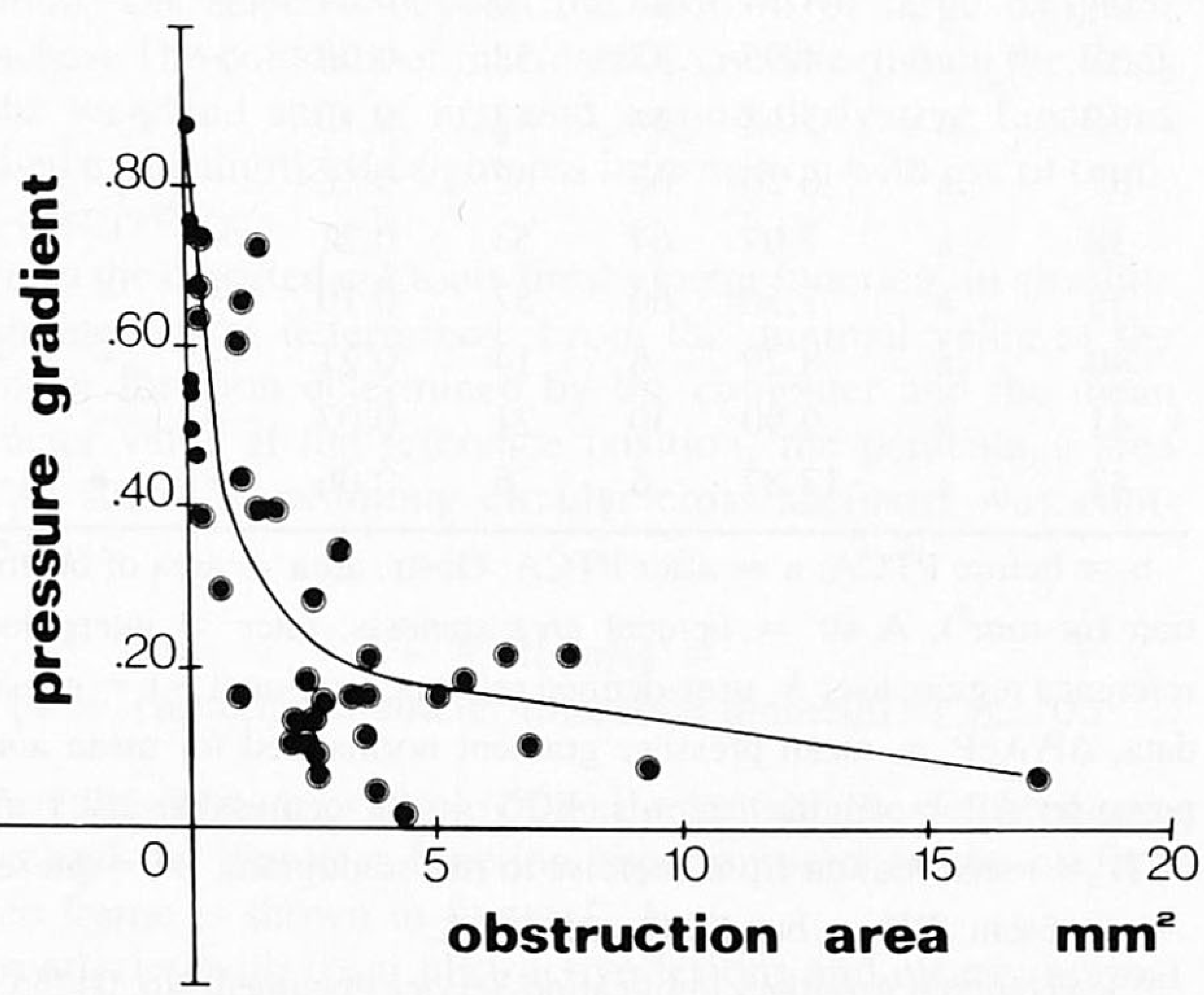

FIGURE 2. The relationship between the mean pressure gradient normalized for the mean aortic pressure and the residual obstruction area (in mm^2) (after subtraction of the area of the angioplasty catheter) is nonlinear; the best fit is obtained by the logarithmic function (r = .74). Filled symbols represent stenoses in which the catheter totally obstructed the vessel.

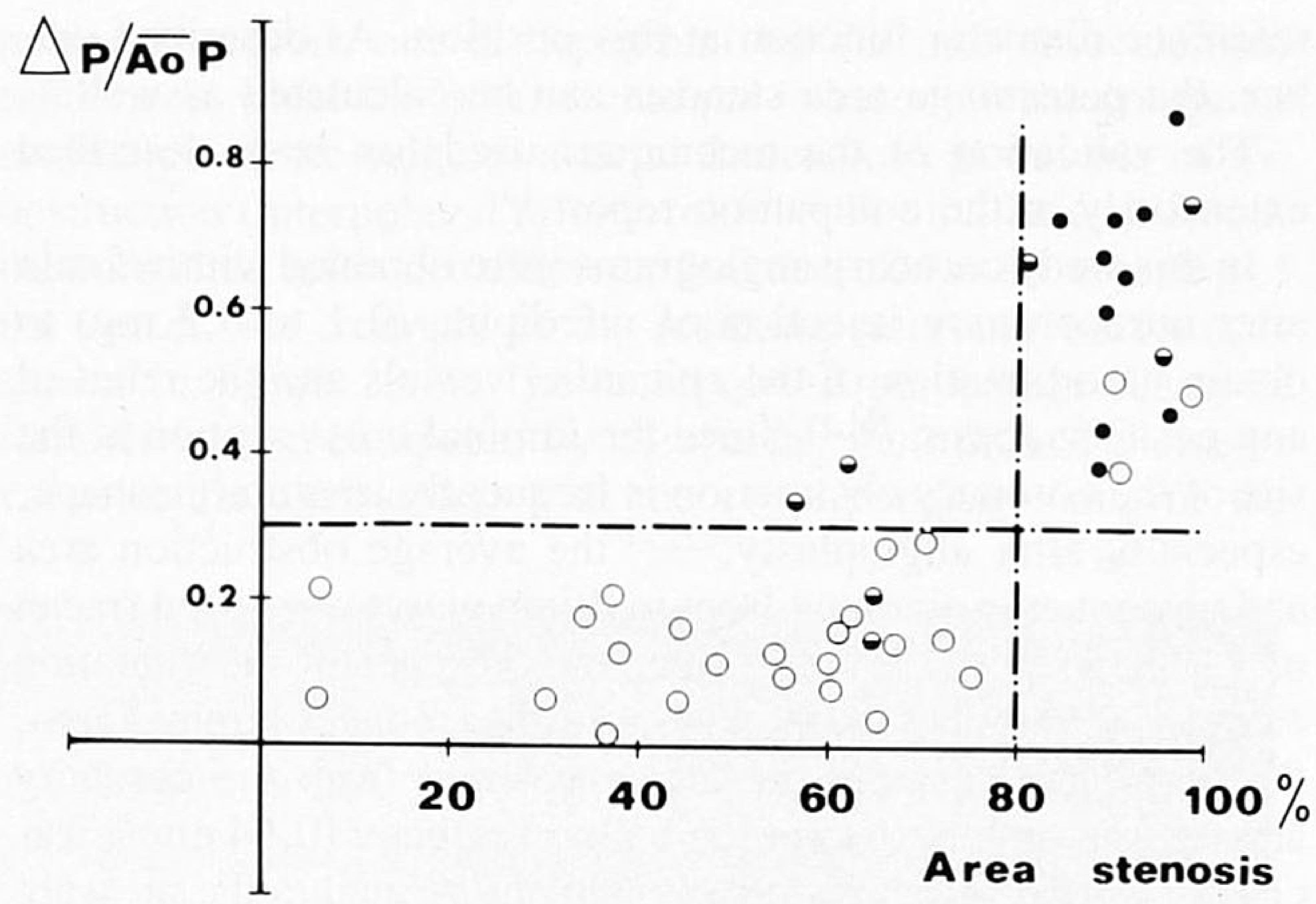

FIGURE 3. The relationships among mean normalized pressure gradient, percentage area stenosis, and the results of thallium scintigraphy are shown. Open circles represent patients with normal scintigrams (group I, n = 25), half-filled circles represent patients with abnormal thallium but normal exercise tests (group II, n = 7), and filled circles represent patients with both abnormal thallium and exercise tests (group III, n = 10).

TABLE 2
Noninvasive test results and angiographic estimates of severity of stenosis

		% Area stenosis	Mean pressure gradient
Group I (Tl−)	25	55 ± 23	0.18 ± 0.13
		NS (I vs II); B (I vs III)	B (I vs II); A (I vs III)
Group II (Tl+/ET−)	7	74 ± 17	0.44 ± 0.23
		NS (II vs III)	NS (II vs III)
Group III (Tl+/ET+)	10	90 ± 4	0.62 ± 0.15

ET = exercise test result; + = abnormal; − = normal; NS = nonsignificant; other abbreviations are as in table 1.
[A]p < .005; [B]p < .001.

the angiographic data in 83% of the patients. An abnormal scintigram was obtained in 13 of the 16 patients with pressure gradients of at least 0.30 and percent areas stenosis greater than or equal to 80% (sensitivity of 81%). Two of three patients with normal thallium uptake and exercise tests had important collaterals apparent on their angiograms. Conversely, thallium uptake was normal in 22 of the 24 patients with pressure gradients less than 0.30 and areas stenosis less than 80% (specificity 92%). Similar figures were found when the user-defined percent area was used instead of the interpolated values (sensitivity 85%, specificity 87%).

Discussion

In this study, we selected the simplest human preparation available to assess the relationship between the angiographic severity of stenosis and the inducibility of regional perfusion defects during exercise thallium scintigraphy. Attempts to correlate closely the anatomy of a coronary stenosis and its physiologic significance are hampered by the large intraobserver and interobserver variability[9, 10] that results from subjective visual scoring of coronary angiograms and from inconstant vasomotor tone. To circumvent these limitations, coronary angiograms were obtained in this study after intracoronary injection of nifedipine and cine films were quantitated with a computerized edge-detection technique. Since part of the results are expressed in terms of percent area (or diameter) of stenosis, a critical point is the one at which the user chooses an appropriate reference area (or diameter). When a large vessel gives rise to a major daughter branch, the cross-sectional area of the main vessel distal to the branch point is significantly less than its area proximal to the branch point; hence, the choice of a proximal reference would not be appropriate. Conversely, the choice of an appropriate distal reference is often hampered by the presence of poststenotic ectasia and by anatomic tapering. Therefore, an alternative method was developed, similar to that used by Crawford et al.,[29] which is based on the computer estimation of the "original contour of the preatherosclerotic lumen" and allows for tapering of the vessel.

The difference in area between the original lumen and the contours of the obstruction is a measure of the atherosclerotic plaque. Crawford et al. have demonstrated that such angiographic assessment of amounts of atherosclerotic plaque by computer densitometry correlated with the cholesterol content in the corresponding human arterial specimen. Their approach includes use of both density and edge measurements; among these, the computer-detected luminal size with taper yields the best correlation with the pathologic data.[29] The data of Crawford et al. pertain to nonbranching segments of femoral arteries; their method has not been validated in coronary arteries in which changes in luminal caliber occur predictably at branching points and not as a result of tapering.[30] In the present as well as in earlier studies,[22, 31] the user-defined and interpolated measurements are closely correlated. However, for the analysis of repeated angiograms,[32, 33] the knowledge of the exact location of the reference region (either proximal or distal to the stenosis) is not required when the interpolated method is used. For these theoretical and practical reasons, we favor the use of an automated definition of the reference area (or diameter) with the interpolated technique.[14, 23]

From these data, obtained in a clinical setting, a curvilinear relationship was found between the pressure drop across the stenosis and the minimal obstruction area as well as the percent cross-sectional area reduction. Both relationships are similar to those calculated on theoretical grounds by Brown et al.[34] as well as to those experimentally derived from isolated human arteries[35] or in canine experiments.[3] Such a curvilinear relationship is expected from the general equation of fluid dynamics showing that a pressure drop across a stenosis is influenced mainly by viscous losses in the stenotic segment and separation losses at the exit of the stenosis. For a given level of flow, the single most important determinant of stenosis resistance is its minimal cross-sectional area, which appears as a second-order term in both viscous and separation loss equations. In the animal laboratory, a coronary stenosis can be characterized precisely by simultaneous measurements of flow and stenotic gradient and related to the quantitative assessment of geometry of stenosis. In such an experimental setting, blood flow velocity and pressure drop across the stenosis are correlated in an exponential fashion.[36]

Recently, coronary blood flow velocity measurements were obtained in patients during heart surgery and related to the results of computer-based analysis of their coronary angiograms.[4, 37] It was shown that the minimal cross-sectional area was the best predictor of the physiologic significance of a coronary stenosis. During cardiac catheterization, the pressure-flow relationship across a coronary stenosis cannot be determined, although the feasibility of transluminal measurements of coronary blood flow velocity has been reported recently.[38] However, the pressure distal to a coronary stenosis is measured routinely during the transluminal angioplasty procedure. This has stimulated the development of very small catheters for the investigation in vivo of the functional significance of pressure gradient measurements.[39] The physiologic value of these measurements, even those obtained with the smallest catheters, must be questioned since the catheter impedes flow through the obstruction. Experimental data obtained in canine femoral arteries suggest that the "true" lesional gradient is overestimated in a predictable manner dependent on the ratio of the diameter of the catheter over that of the stenosis.[40] In addition, the mean pressure gradient is affected by phasic changes in flow velocity.[36] The distal coronary pressure may be affected by collaterals and is entirely determined by collateral flow when the catheter used for angioplasty totally obstructs the vessel. In spite of these limitations, Vogel et al.[41] have shown that the mean pressure gradient measured across the stenosis during angioplasty predicted accurately the coronary flow reserve measured by digital angiography, as the ratio of hyperemia over control myocardial contrast appearance time. In the present study, the gradient was related in a curvilinear way to the actual luminal area obtained by subtracting the area of the deflated balloon catheter from the minimal obstruction area as assessed by quantitative angiography.

The major finding of this study was that the combination of pressure drop measurements across the stenosis, with quantitative assessment of luminal narrowing, predicted the occurrence of exercise thallium perfusion abnormalities better than did the measurement of the stenotic area alone. With the cutoff values of 0.30 for the pressure gradient and 80% for the percent reduction in cross-sectional area, the results of exercise thallium scintigraphy were correctly predicted from the angiographic data in all but six patients. In four of these, thallium perfusion abnormalities occurred without signs of ischemia in the presence of a noncritical cross-sectional stenosis area of about 60%. These discrepancies are not surprising since many other factors, such as blood density, viscosity, length of stenosis, and divergence angle were not accounted for.[34, 35] Two patients had normal scintigrams and exercise test results although ischemia was expected from the angiographic measurements. This could be the result of the presence of coronary collaterals, as apparent on their angiograms, since previous work suggests that their presence can prevent the occurrence of thallium perfusion defects during exercise.[42, 43]

In summary, the functional significance of coronary stenosis can be evaluated in patients at rest by quantitative analysis of coronary dimensions and transstenotic pressure gradient measurements. In patients with single-vessel disease of the left anterior descending coronary artery this allowed identification, while they were at rest, of those lesions responsible for thallium perfusion defects induced by exercise.

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