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Which Cineangiographically Assessed Anatomic Variable Correlates Best With Functional Measurements of Stenosis Severity? A Comparison of Quantitative Analysis of the Coronary Cineangiogram With Measured Coronary Flow Reserve and Exercise/Redistribution Thallium-201 Scintigraphy

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The goal of this investigation was to establish which measured anatomic variable of stenotic coronary lesions correlates best with functional severity. Therefore, 38 patients with single vessel disease underwent coronary cineangiography and exercise/redistribution thallium-201 scintigraphy. The computer-based Cardiovascular Angiography Analysis System was used to determine the cross-sectional area at the site of obstruction (OA) and percent diameter stenosis (DS), and to calculate the pressure drop over the stenosis (PD) with use of fluid dynamic equations. Coronary flow reserve was measured radiographically. Myocardial perfusion defects on thallium scintigrams were analyzed quantitatively and by visual interpretation.

The relations between coronary flow reserve (CFR) and the three anatomic variables were described by the following equations: 1) CFR = 4.6 − 0.053 DS, r = 0.82; SEE: 0.79, p < 0.001. 2) CFR = 0.5 + 0.75 OA, r = 0.87; SEE: 0.68, p < 0.001. 3) CFR = 3.6 − 1.5 log PD, r = 0.90; SEE: 0.62, p < 0.001.

The calculated pressure drop was highly predictive of the thallium scintigraphic results with a sensitivity of 94% and a specificity of 90%. The calculated pressure drop is a better anatomic variable for assessing the functional importance of a stenosis than is percent diameter stenosis or obstruction area. However, the 95% confidence limits of the relation between pressure drop and coronary flow reserve are wide, making the measurement of coronary flow reserve an indispensable addition to quantitative angiography, especially when determining the functional importance of moderately severe coronary artery lesions.

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Visual interpretation of the coronary cineangiogram inadequately predicts the physiologic importance of obstructive coronary artery disease (1). Computer-based quantitative analysis has helped minimize the problems of high interobserver and intraobserver variability in the assessment of the anatomic severity of a coronary obstruction (2), and allows the calculation of the pressure-flow characteristics of a coronary stenosis (3). Exercise/redistribution thallium-201 perfusion scintigraphy has been used extensively as a noninvasive means to study the functional consequences of a coronary artery stenosis (4–6). Recently, the concept of coronary flow reserve has been introduced as a physiologic measurement of stenosis severity (7,8), and the development of digital angiographic techniques has made this measurement possible during cardiac catheterization (9,10). In a previous study (10) we investigated the relation between minimal cross-sectional obstruction area, percent area stenosis and coronary flow reserve. We found a considerable scatter of the data despite excellent overall correlations between these two quantitative angiographic variables and coronary flow reserve. Approaches that integrate all angiographically determined dimensions of an obstruction, such as the calculated pressure drop over the stenosis, are attractive as they may allow a better angiographic description of functional stenosis severity (10,11).

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The goal of this investigation was to study which quantitative cineangiographic variable correlates best with functional measurements of stenosis severity. We compared percent diameter stenosis, minimal cross-sectional obstruction area and calculated pressure drop across the stenosis with radiographically measured coronary flow reserve and results from exercise/redistribution thallium-201 perfusion scintigraphy.

Methods

Study patients. Thirty-eight patients with single vessel coronary artery disease were studied. The diseased vessel was the left anterior descending coronary artery in 30 patients, the left circumflex coronary artery in 5 and the right coronary artery in 3. Their mean age was 53 years (range 31 to 68); 34 patients (89%) were male. Coronary cineangiography was performed as part of an ongoing restenosis study after percutaneous transluminal coronary angioplasty (28 patients) or to evaluate a chest pain syndrome (10 patients). Informed consent was obtained for the additional investigations.

All patients were studied without premedication, but their medical treatment was continued on the day of the investigation (a calcium channel antagonist and an antiplatelet agent in the 28 patients studied after angioplasty; nitrates, calcium antagonists and beta-adrenergic blockers in the remaining 10 patients). Left ventriculography was performed in all patients and showed normal systolic and diastolic wall motion with an ejection fraction >55%. Patients with systemic hypertension, cardiac hypertrophy, documented previous myocardial infarction, valvular heart disease, angiographic evidence of collateral circulation and anemia or polycythemia were excluded as these conditions may influence coronary flow reserve (12–14).

Exercise thallium scintigraphy. The patients performed a symptom-limited exercise test on a bicycle ergometer with stepwise increments of 20 W/min on the day before the cardiac catheterization. All patients exercised to >80% of their expected normal exercise capacity (corrected for age, gender and height). This procedure has previously been described (15–17). One minute before maximal exercise, 1.5 mCi thallium-201 was administered. Planar imaging was started 3 min later in three views: anterior and 45° and 65° left anterior oblique. These same static planar images were repeated at rest 4 h later (redistribution imaging). The exercise and redistribution images were processed on a DEC gamma-11 system with a quantification procedure developed at our institution (15,16). All images were spatially registered in the computer on the basis of the detected positions of point sources defined with a cobalt marker pen at two positions on the patient's chest. After automated left ventricular contour detection and interpolative background correction, exercise, redistribution and washout circumferential profiles were computed at 6° intervals (quantitative thallium perfusion analysis). The late circumferential profiles were normalized to a delay of 4 h between the early and late images. The profiles of the early and late images were normalized to 100% and compared with normal values defined by the 10th and 90th percentiles of the profiles of a group of individuals without apparent heart disease.

Semiquantitative thallium uptake in all regions was scored both in the immediate postexercise and late images on a three point scale. The scores of regions related to the diseased coronary artery were summed per patient and the difference between the postexercise and late images was taken as a measure of the amount of redistribution between the postexercise and late images. The analog images from the gamma camera (Polaroid), the background-corrected images and the circumferential profiles were interpreted prospectively on a routine basis by three experienced observers without knowledge of the angiographic data. Transient and persistent defects were considered abnormal (15,16).

Quantitative coronary cineangiography. The coronary artery dimensions were determined with the computer-based Cardiovascular Angiography Analysis System (CAAS) (2,10,18). In essence, the boundaries of a selected coronary artery segment were detected automatically from optically magnified and video digitized regions of interest of a cineframe. Calibration of the diameter data in absolute values (millimeters) was achieved by detecting the boundaries of a section of the contrast catheter and comparing the mean diameter in pixels with the known size in millimeters (19). The contour positions of the arterial and catheter segments were corrected for the pincushion distortion (18). A computer estimation of the original arterial dimensions at the site of obstruction was used to define the reference region (18). The interpolated percent diameter stenosis and the minimal obstruction area (mm^2) were calculated by averaging the values from at least two, preferably orthogonal, angiographic views. The length of the obstruction was assessed from curvature analysis of the derived diameter function. A mean of 2.3 angiographic views per patient was used in this study.

The theoretical pressure drop for a hyperemic flow of three times coronary blood flow at rest was calculated according to the following hemodynamic equation (10,11, 20): $PD = f\,Q + s\,Q^2$, where PD = pressure drop, f = coefficient of viscous resistance and s = coefficient of separation resistance. Volume flow was calculated from the interpolated reference cross-sectional area, assuming a coronary blood flow velocity of 15 cm/s.

Coronary flow reserve measurements. The coronary flow reserve measurement with digital subtraction cineangiography from 35 mm cinefilm has been implemented on the CAAS (10). The heart was atrially paced at a rate just above the spontaneous heart rate. An electrocardiographicallytriggered injection into the coronary artery was made with a fixed amount of Jopamidol through a Medrad Mark IV infusion pump. The injection rate of the contrast medium was judged to be adequate when back flow of contrast medium into the aorta occurred. The angiogram was repeated 30 s after pharmacologically induced hyperemia by a bolus injection of 12.5 mg papaverine into the coronary artery (10,21). Five 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 contrast administration was chosen as the mask. From the sequence of background-subtracted images, a contrast arrival time image was determined, with the use of an empirically derived fixed density threshold (10). In addition to the contrast arrival time image, a density image was computed, with each pixel intensity value being representative for the maximal local contrast medium accumulation.

Coronary flow reserve (CFR) was then calculated as:

$$CFR = \frac{Qh}{Qb} = \frac{Dh}{Th} : \frac{Db}{Tb},$$

where Q is regional blood flow, D is the mean contrast density and T the mean appearance time at baseline (b) and hyperemia (h). Mean contrast medium appearance time and density were computed within user-defined regions of interest that were chosen in such a way that the epicardial coronary arteries visible on the angiogram, the coronary sinus and the great cardiac vein were excluded from the analysis. Normal values for coronary flow reserve in our laboratory have been established. In 24 patients (a study in 12 has been published previously [10]) with normal coronary arteries and absence of factors known to decrease vascular reserve, the coronary flow reserve (mean ± SD) was 5.0 ± 0.8. Therefore, coronary flow reserve is defined as normal when ≥3.4.

Statistical analysis. Least squares linear and nonlinear regression analyses were used to define the best-fit relations between the quantitative cineangiographic variables and coronary flow reserve. The differences between the measured coronary flow reserve and the best fit relations were compared with variance analysis and the Student *t* test for paired observations, to determine which quantitative angiographic variable correlates best with coronary flow reserve.

Results

Angiographic and thallium scintigraphic results. On angiography, the measured coronary flow reserve ranged from 0.4 to 5.5. The interpolated reference area ranged from 2.9 to 9.4 mm^2, the length of the stenotic lesions from 3.2 to 18.6 mm, the obstruction area from 0.4 to 6.8 mm^2 and the

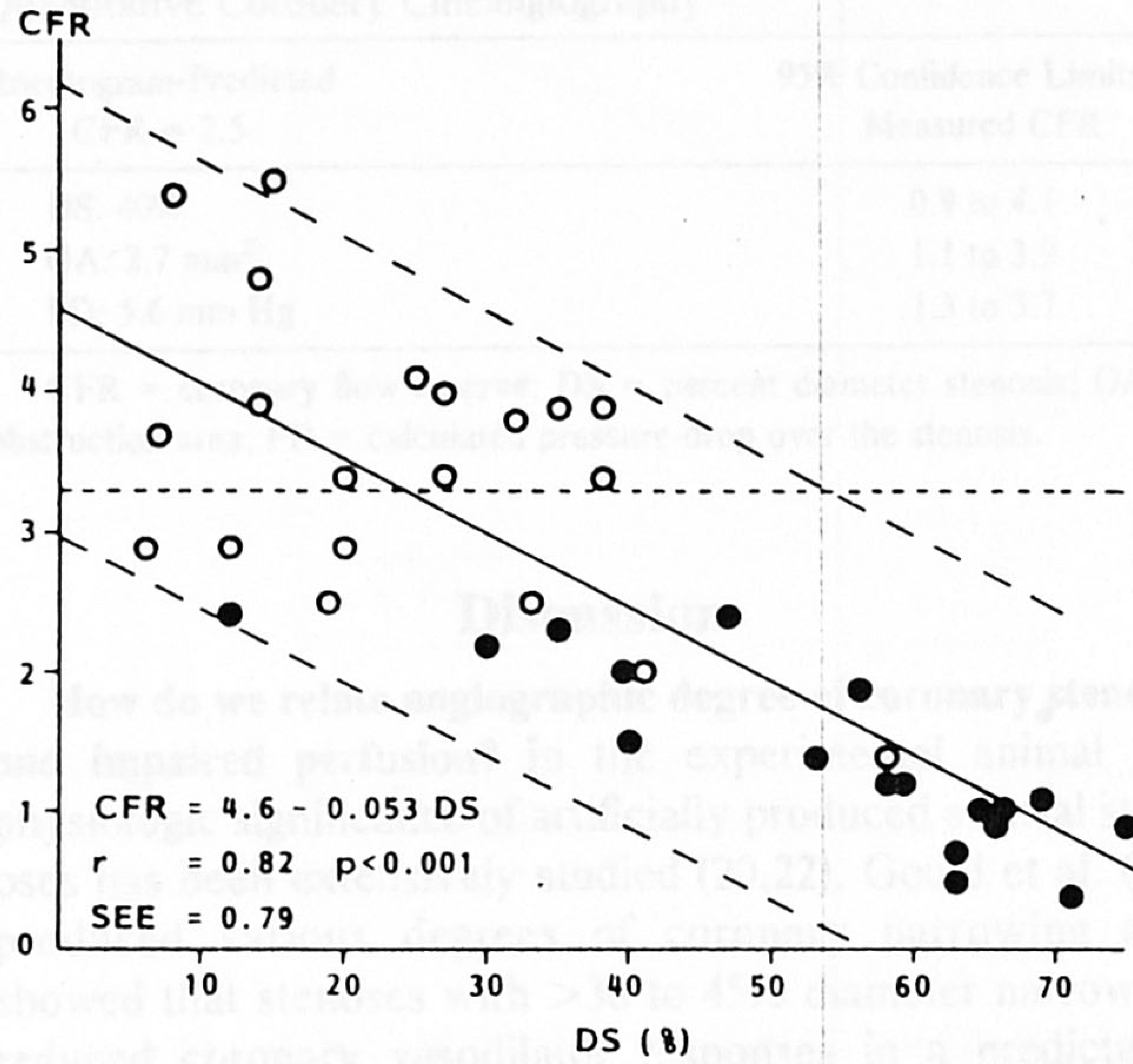

Figure 1. Relation between coronary flow reserve (CFR), thallium scintigraphy and percent diameter stenosis (DS) in 38 patients. The **dashed horizontal line** is the lower limit of normal coronary flow reserve. The **black circles** represent 18 patients with a positive thallium scintigram. The **open circles** represent 20 patients with a negative thallium scintigram.

diameter stenosis from 6 to 75%. The calculated pressure drop ranged from 0.3 to 144 mm Hg.

The thallium uptake score ranged from 0 to 12 on the postexercise images and from 0 to 8 on the late images. The difference in score between postexercise and late images (redistribution) ranged from 0 to 10. The quantitative analysis of the circumferential postexercise and late thallium images revealed a mean defect on the postexercise image of 157 (range 0 to 1094), and 68 (range 0 to 399) on the late image, with a mean difference (redistribution) of 89 (range 0 to 1081). The final result of the thallium analysis procedure was that the three observers judged 18 thallium scintigrams to indicate exercise-induced ischemia. The sensitivity and specificity of thallium scintigraphy to detect patients with an abnormal coronary flow reserve (<3.4) were 68% (17 of 25) and 100% (18 of 18), respectively.

Relations among percent diameter stenosis, obstruction area, calculated pressure drop and measured coronary flow reserve. These relations were best described by the following equations: The relation between coronary flow reserve (CFR) and percent diameter stenosis (DS): CFR = 4.6 − 0.053 DS, ($r = 0.82$, SEE: 0.79, $p < 0.001$) (Fig. 1). The relation between coronary flow reserve and obstruction area (OA): CFR = 0.75 OA + 0.5, ($r = 0.87$, SEE: 0.68, $p < 0.001$) (Fig. 2). The relation between coronary flow reserve and the calculated pressure decrease (PD): CFR = 3.6 − 1.5 log PD, ($r = 0.90$, SEE: 0.62, $p < 0.001$) (Fig. 3). The calculated pressure drop correlated significantly better (p <

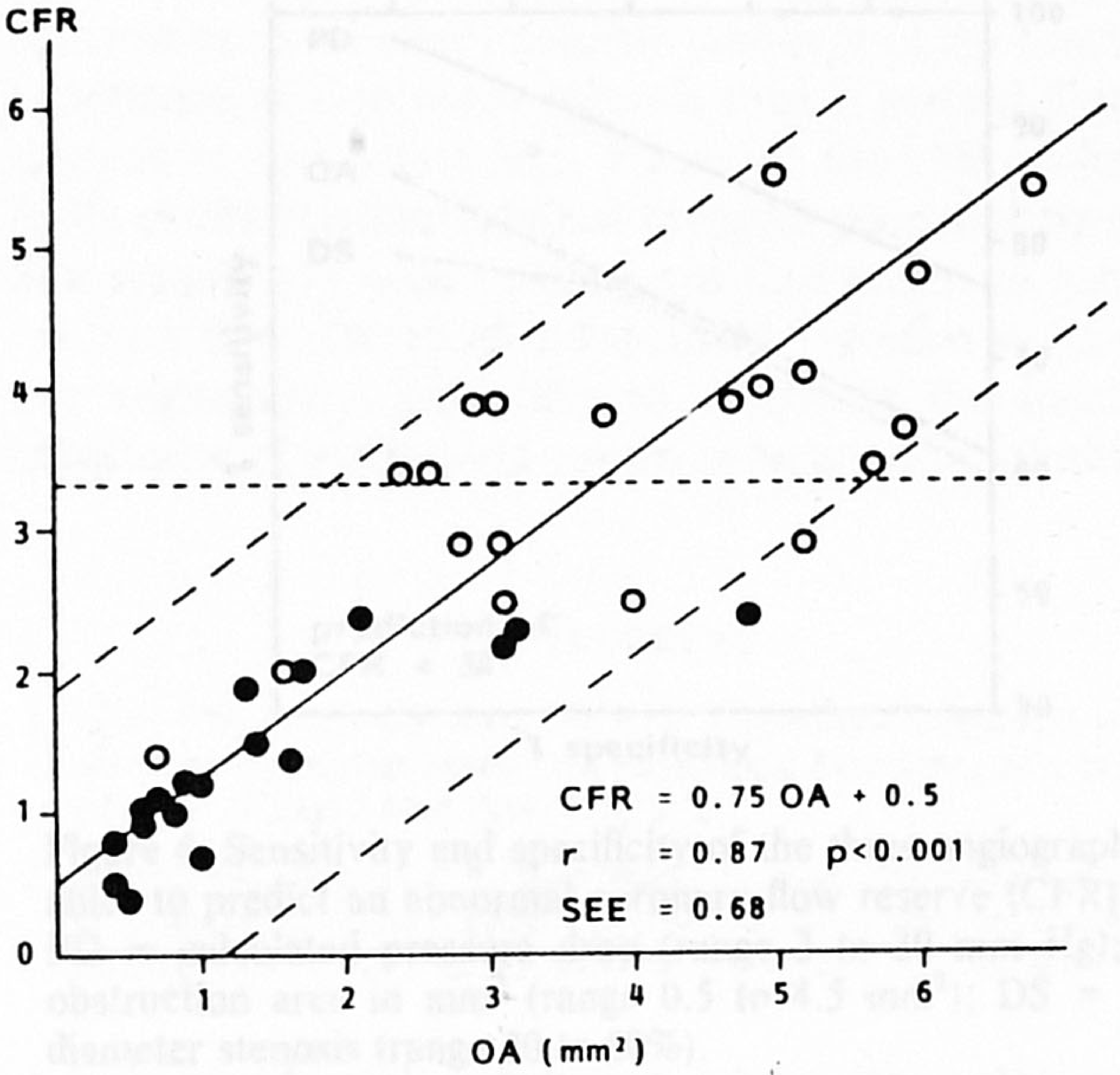

Figure 2. Relation between coronary flow reserve (CFR), thallium scintigraphy and cross-sectional obstructive area (OA). Format as in Figure 1.

0.05) with measured coronary flow reserve than with percent diameter stenosis and obstruction area.

The predictive value of the three angiographic variables in relation to the measured coronary flow reserve is shown in Table 1 by giving the 95% confidence intervals for a predicted coronary flow reserve of 2.5. The sensitivity and specificity of the three angiographic variables in identifying patients with an abnormal measured coronary flow reserve are shown in Figure 4 and in identifying patients with a positive thallium scintigram in Figure 5.

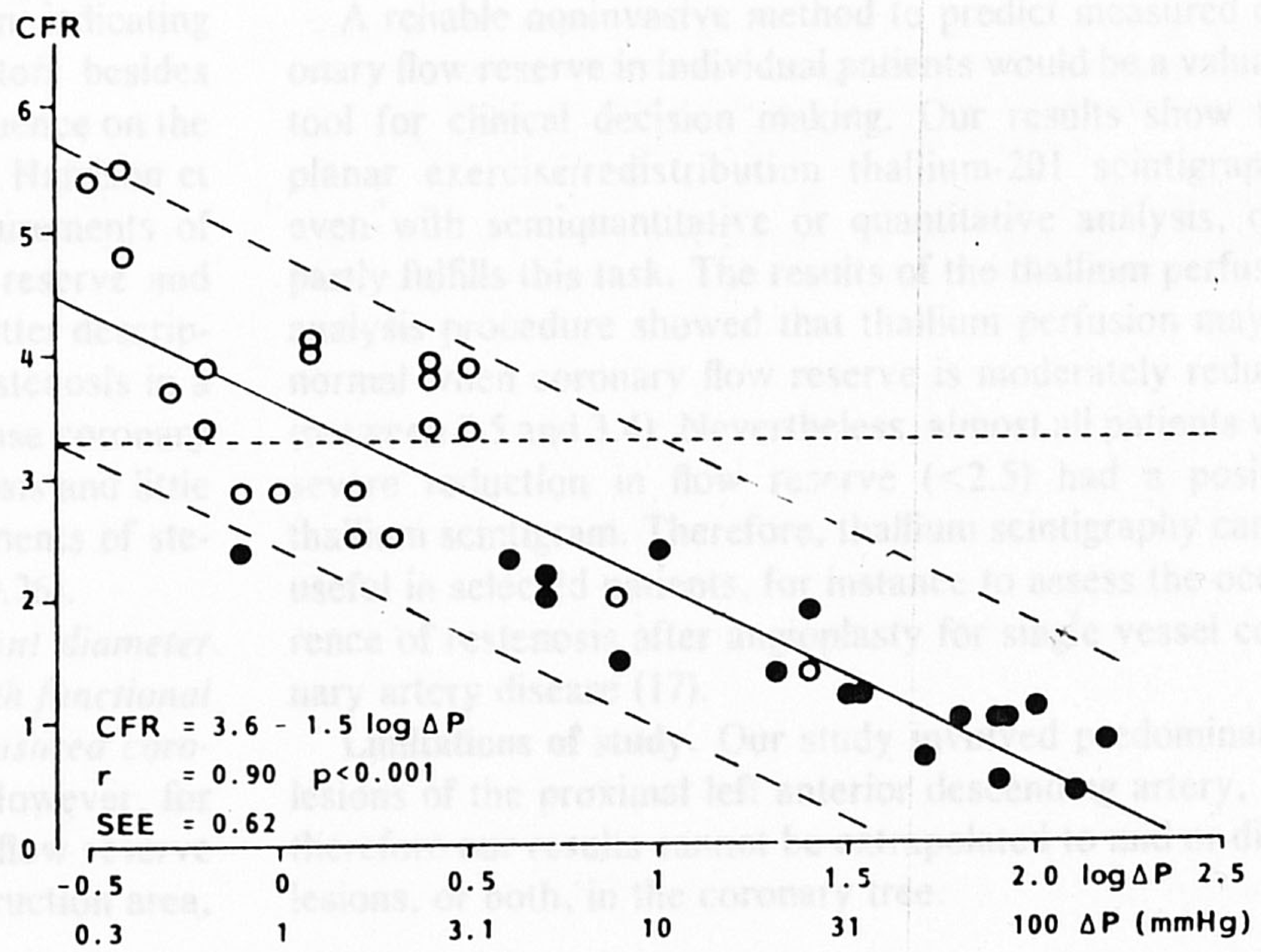

Figure 3. Relation between coronary flow reserve (CFR), thallium scintigraphy and calculated pressure drop (ΔP). Format as in Figure 1.

Table 1. Prediction of Measured Coronary Flow Reserve With Quantitative Coronary Cineangiography

Roentogram-Predicted CFR = 2.5	95% Confidence Limits of Measured CFR
DS: 40%	0.9 to 4.1
OA: 2.7 mm²	1.1 to 3.9
PD: 5.6 mm Hg	1.3 to 3.7

CFR = coronary flow reserve; DS = percent diameter stenosis; OA = obstruction area; PD = calculated pressure-drop over the stenosis.

Discussion

How do we relate angiographic degree of coronary stenosis and impaired perfusion? In the experimental animal the physiologic significance of artificially produced arterial stenoses has been extensively studied (20,22). Gould et al. (22) produced various degrees of coronary narrowing and showed that stenoses with >30 to 45% diameter narrowing reduced coronary vasodilator responses in a predictable fashion. However, in human beings with coronary artery disease, the relation between the visually estimated percent diameter stenosis and the consequent reduction in coronary flow reserve is poor (1). The two basic problems that have hampered the assessment of the relation between the angiographic degree of stenosis and the actual impairment of perfusion, now seem to have been solved by new technical developments. First, the recent description (9,10) of a technique that uses digital subtraction has rendered the assessment of regional coronary flow reserve possible during cardiac catheterization. Second, the visual assessment of the coronary angiogram with its large intraobserver and interobserver variability has made way for computer-based quantitative analysis of the coronary angiogram including auto-

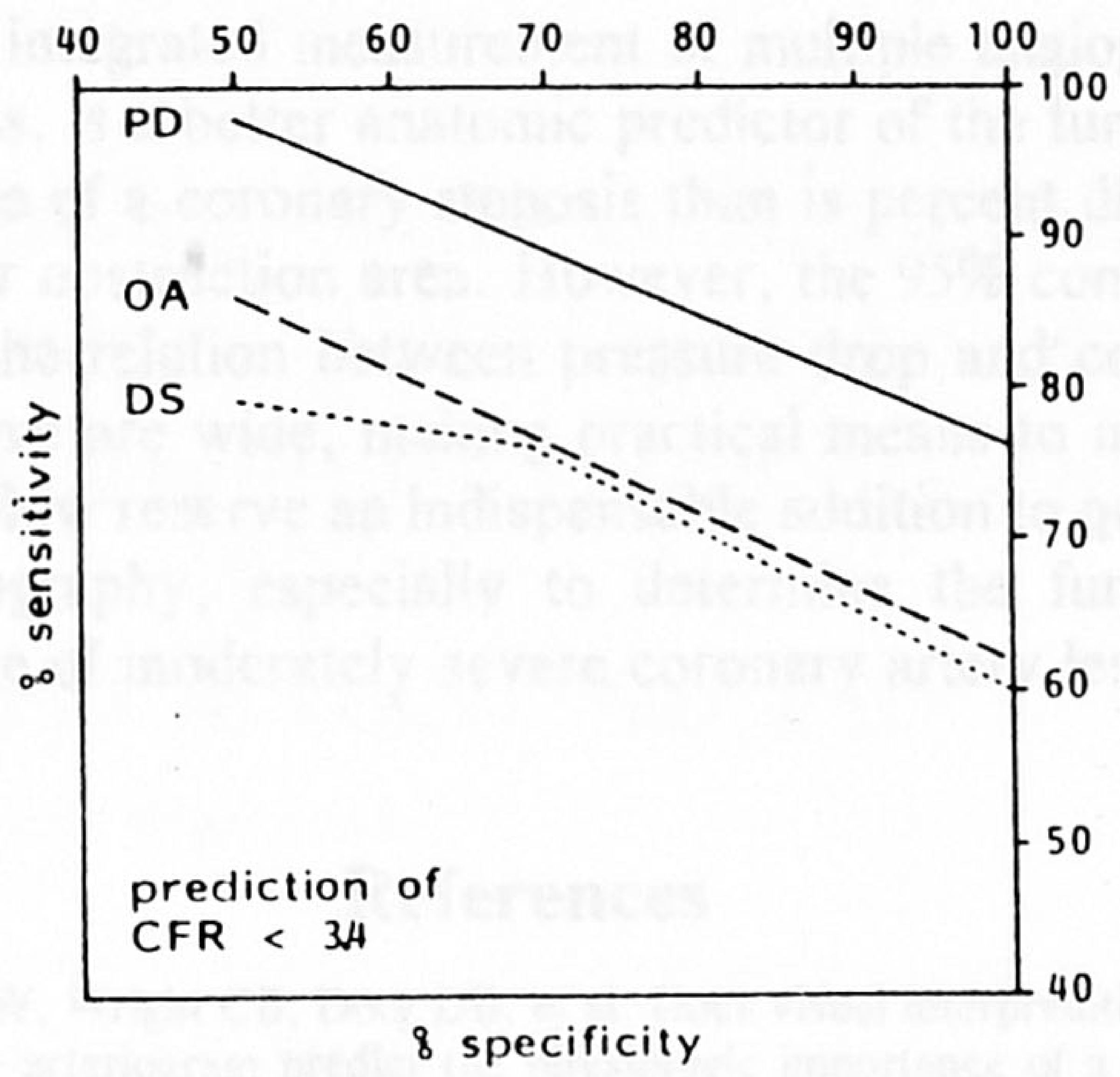

Figure 4. Sensitivity and specificity of the three angiographic variables to predict an abnormal coronary flow reserve (CFR) (<3.4). PD = calculated pressure drop (range 3 to 30 mm Hg); OA = obstruction area in mm^2 (range 0.5 to 4.5 mm^2); DS = percent diameter stenosis (range 30 to 60%).

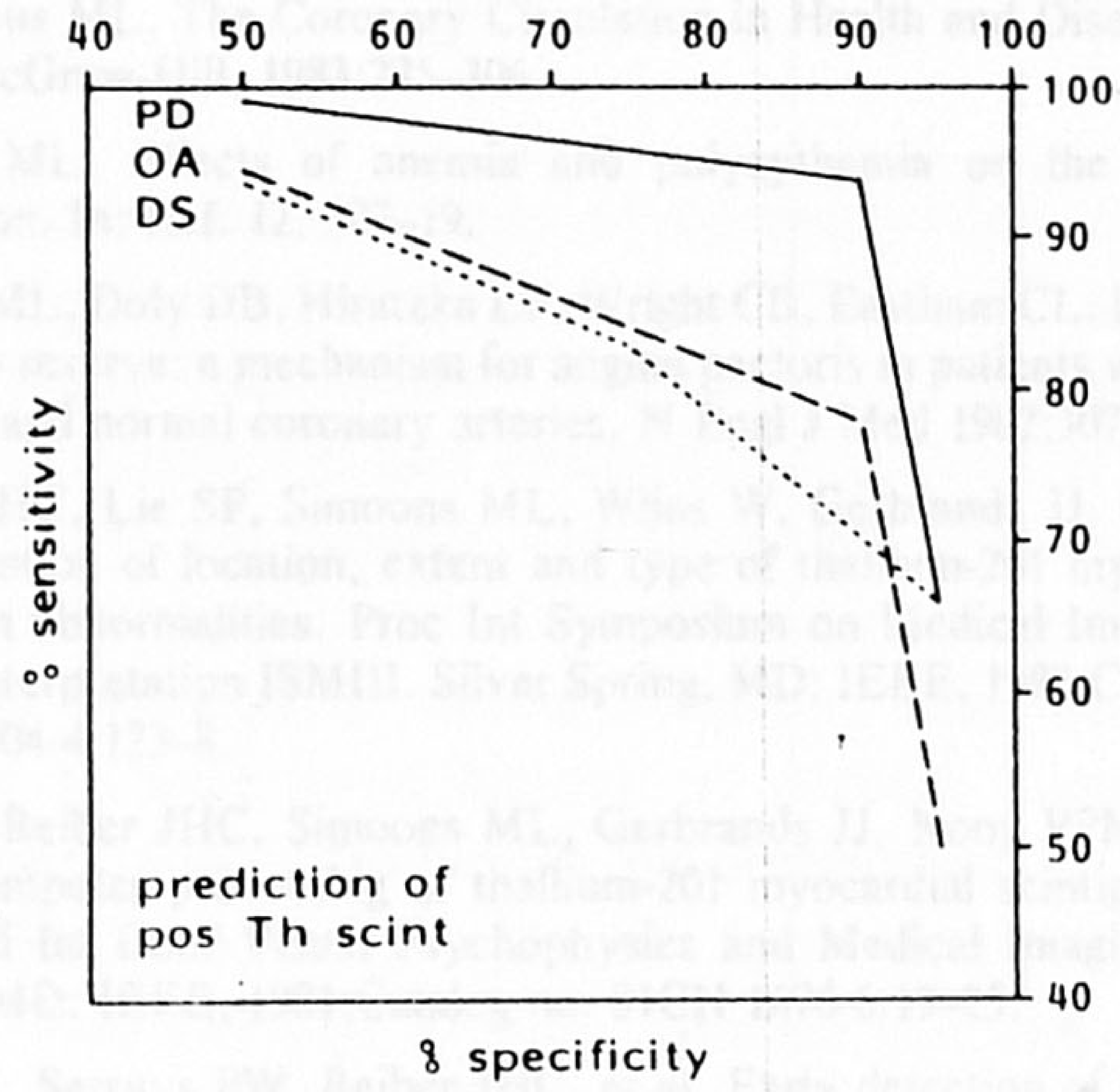

Figure 5. Sensitivity and specificity of the three angiographic variables to predict a positive thallium scintigram (pos Th scint). Abbreviations as in Figure 4.

mated contour detection, which improves accuracy and allows for the precise determination of most dimensions of a given stenosis in a coronary artery (2,18).

Description of stenosis severity. The measurement of percent diameter narrowing is the most commonly employed descriptor of stenosis severity, but its use has several disadvantages. First, McPherson et al. (23) documented that substantial diffuse intimal atherosclerosis is often present, even when the angiogram reveals only a discrete lesion. This factor may make the estimation of the normal dimensions of a coronary artery impossible and precludes the use of relative measures of stenosis severity; it may explain why 12 of our patients with a percent diameter stenosis <50% had a (moderately) reduced coronary flow reserve. The obstruction area (mean ± SD) of these patients was 3.0 ± 1.0. Six of these patients also had a thallium scintigram indicating exercise-induced ischemia. Second, many factors besides percent diameter stenosis have a significant influence on the pressure-flow characteristics of a stenosis (24). Harrison et al. (25) compared relative and absolute measurements of stenosis severity with coronary flow velocity reserve and concluded that obstruction area (mm^2) was a better descriptor of stenosis severity than was percent area stenosis in a patient population with probable extensive diffuse coronary artery disease. In patients with a discrete stenosis and little diffuse disease, relative and absolute measurements of stenosis severity convey the same information (10,26).

The present study confirms that both percent diameter stenosis and obstruction area correlate well with functional measurements of stenosis severity such as measured coronary flow reserve and thallium scintigraphy. However, for individual patients the prediction of coronary flow reserve with the use percent diameter stenosis or obstruction area, or both, is limited by the wide 95% confidence intervals (Table 1). Wilson et al. (26) reported a comparable correlation between these two parameters and flow reserve with similar wide 95% confidence intervals. Approaches that integrate several angiographic dimensions are conceptually attractive and have been validated in dogs (11). The 95% confidence limits of the relation between pressure drop and coronary flow reserve are less than those between obstruction area or percent diameter stenosis and coronary flow reserve. This fact indicates that the calculated pressure drop over the stenosis as an integrated measurement of multiple angiographic variables is indeed a more accurate anatomic description of the functional consequences of a coronary artery lesion. The calculated pressure drop is a better variable to differentiate patients with normal from those with abnormal coronary flow reserve and predicts the results of thallium scintigraphy more accurately.

A reliable noninvasive method to predict measured coronary flow reserve in individual patients would be a valuable tool for clinical decision making. Our results show that planar exercise/redistribution thallium-201 scintigraphy, even with semiquantitative or quantitative analysis, only partly fulfills this task. The results of the thallium perfusion analysis procedure showed that thallium perfusion may be normal when coronary flow reserve is moderately reduced (between 2.5 and 3.4). Nevertheless, almost all patients with severe reduction in flow reserve (<2.5) had a positive thallium scintigram. Therefore, thallium scintigraphy can be useful in selected patients, for instance to assess the occurrence of restenosis after angioplasty for single vessel coronary artery disease (17).

Limitations of study. Our study involved predominantly lesions of the proximal left anterior descending artery, and therefore our results cannot be extrapolated to mid or distal lesions, or both, in the coronary tree.

Conclusions. The calculated pressure drop over a stenosis, as an integrated measurement of multiple angiographic dimensions, is a better anatomic predictor of the functional importance of a coronary stenosis than is percent diameter stenosis or obstruction area. However, the 95% confidence limits of the relation between pressure drop and coronary flow reserve are wide, making practical means to measure coronary flow reserve an indispensable addition to quantitative angiography, especially to determine the functional importance of moderately severe coronary artery lesions.

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