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Which Angiographic Variable Best Describes Functional Status 6 Months After Successful Single-Vessel Coronary Balloon Angioplasty?

BENNO J. RENSING, MD, WALTER R. M. HERMANS, MD, JAAP W. DECKERS, MD, PIM J. DE FEYTER, MD, FACC, PATRICK W. SERRUYS, MD, PHD, FACC

Rotterdam, The Netherlands

Objectives. The aim of this study was to determine which quantitative angiographic variable best describes functional status 6 months after coronary balloon angioplasty.

Background. Several angiographic restenosis criteria have been developed. These can be divided into those that describe the *change* in lesion severity and those that merely describe lesion severity at follow-up angiography. The functional significance of these criteria is unknown.

Methods. We studied 350 patients with single-vessel coronary artery disease who underwent a single-site balloon dilation. Sensitivity and specificity curves were constructed for the prediction of anginal status and exercise electrocardiography of four quantitative angiographic variables that describe restenosis. The point of highest diagnostic accuracy for the variables was determined at the intersection of the sensitivity and specificity curves. Results of exercise electrocardiography were considered indicative for ischemia 6 months after angioplasty if horizontal or downsloping ST segment depression ≥1 mm occurred.

Results. The points of highest diagnostic accuracy of the angiographic variables were similar for both anginal status and exercise electrocardiography: 1.45 and 1.46 mm for the minimal lumen diameter measurements, 45.5% and 46.5% for the percent diameter stenosis measurements at follow-up, −0.30 and −0.32 mm for change in minimal lumen diameter and −10% and −10% for the change in percent diameter stenosis at follow-up.

Conclusions. Angiographic variables reflecting a change in lesion severity at follow-up angiography were only slightly less accurate than variables that describe lesion severity at follow-up. The large study group and the fact that the same optimal values for diagnostic accuracy of the various quantitative angiographic variables were obtained for the prediction of two different markers of ischemia suggests that these values reflect the lesion severity or increase in lesion severity in major epicardial vessels at which coronary flow reserve is unable to meet myocardial demands.

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Soon after the introduction of percutaneous transluminal coronary balloon angioplasty the vexing problem of restenosis became apparent. Approximately 30% to 40% of patients will show functional or angiographic signs, or both, of restenosis in the first months after a successful angioplasty procedure. A multitude of angiographic restenosis criteria have been developed over the last 12 years (1). Restenosis criteria currently in use can be divided in to those that describe the change in lesion severity from the postangioplasty situation up to the follow-up angiogram and those that merely describe lesion severity at follow-up angiography. An example of the first category is the loss in lumen diameter of >0.72 mm as proposed by Serruys et al. (2), and an example of the latter category is the criterion of >50% diameter stenosis at follow-up. Criteria that describe a change in lumen diameter may ignore the functional significance of the lesion at follow-up, especially in large vessels (3), whereas criteria that only describe the situation at follow-up will preselect lesions with a suboptimal result after angioplasty and thereby disregard the magnitude of the reactive intimal hyperplasia (1). Recurrence of a flow-limiting stenosis can usually be identified by symptoms of chest pain similar to those that occurred before angioplasty. In addition to the medical history, exercise electrocardiographic (ECG) testing is generally performed as a noninvasive approach to confirm the recurrence of a coronary artery obstruction because it is a relatively simple, safe and inexpensive test. To determine which quantitative angiographic variable best predicts the functional status of the individual patient, we studied the recurrence of anginal complaints and positive ECG exercise test results 6 months after successful angioplasty in a selected patient group with single-vessel disease and single-site dilation. The functional variables (recurrence of angina and a positive exercise test result) were correlated with quantitative angiographic variables of change in lesion severity (change in minimal lumen diameter, change in percent diameter stenosis) and variables that merely describe lesion severity at follow-up angiography (minimal lumen diameter and percent diameter stenosis).

From the Thoraxcenter, Erasmus University, Rotterdam, The Netherlands.

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Address for correspondence: Patrick W. Serruys, MD, PhD, Catheterization Laboratory, Thoraxcenter, Erasmus University, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.

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Methods

Study group. The original patient group consisted of 697 patients who were enrolled in the multicenter CARPORT trial. A list of participating centers and investigators has been published previously (4). In this randomized trial a thromboxane A_2 receptor antagonist (GR32191B) was clinically tested against placebo for its ability to prevent restenosis after primary coronary angioplasty. Identical angiographic, clinical and exercise test outcomes were observed in both randomization groups, so that the placebo and active treatment groups were pooled for the present study (4). Antianginal medication during follow-up was not standardized after the procedure but was also comparable in the two treatment groups. Selection criteria for this trial have been published previously (4). Of the 697 patients, 649 had a successful procedure, defined as a <50% residual stenosis by visual inspection of the postangioplasty angiogram and no occurrence of in-hospital complications (death, acute myocardial infarction, bypass grafting, repeat angioplasty or symptom recurrence). Five hundred seventy-five patients had subsequent follow-up angiograms that were suitable for quantitative analysis (follow-up rate 88.6%). Of these 575 patients, 350 had single-vessel coronary artery disease and underwent a single-site dilation and therefore it was presumed that complete revascularization was achieved in this group of patients. All patients gave written informed consent and the study protocol was approved by the institutional review boards of the participating centers.

Angioplasty procedure and follow-up angiography. Coronary angioplasty was performed with a steerable, movable guide wire system by the femoral route. Details of the procedure have been described previously (4).

Three coronary angiograms were obtained in each patient, one just before angioplasty, one immediately after and one at 6-month follow-up after angioplasty. The angiograms were recorded so that they were suited for quantitative analysis by the computer-assisted Cardiovascular Angiography Analysis System (CAAS) (5–7). All necessary details of the procedure were recorded and drawings of the segments to be analyzed were made. For calibration purposes the catheter tips were cut off for later measurement with a microcaliper. To standardize the method of data acquisition and to ensure exact reproducibility of the angiographic studies, measures were taken as described previously (4,8,9). All angiograms were processed and analyzed in a central core laboratory. The follow-up coronary angiogram was performed at 6-month follow-up or earlier if symptoms recurred before 6 months. If no definite restenosis was present and the follow-up time was <4 months, the patient was asked to undergo another coronary arteriogram at 6 months.

Quantitative angiography. All cineangiograms were analyzed with the CAAS system (5–7). In this system, a computer-derived reconstruction of the original arterial dimension at the site of obstruction (assuming no disease is present) is used to define the interpolated reference diameter. In case of a total occlusion, a value of 0 for the minimal lumen diameter and 100% for the percent diameter stenosis was substituted. The mean change in minimal lumen diameter from postangioplasty angiography to follow-up angiography and from preangioplasty to postangioplasty was derived from matched angiographic projections.

Follow-up evaluation and bicycle ergometry. Each patient was seen in the outpatient clinic for an interview, physical examination and a symptom-limited exercise test 1 to 4 days before follow-up catheterization. Assessment of anginal complaints and test evaluation were documented at the individual centers before repeat angiography and thus without knowledge of the coronary anatomy. Typical anginal complaints were classified according to the Canadian Cardiovascular Society angina classification. The exercise test was performed on a bicycle ergometer according to two different protocols. In Berlin the test was performed with the patient supine, starting with a work load of 25 W that increased by 25 W every 2 min. In the other five participating clinics the test was performed with the patient seated, starting with a work load of 20 W that was increased by 20 W every min. Exercise was continued until anginal symptoms, a decrease in systolic blood pressure, severe arrhythmia, or horizontal or downsloping ST segment depression >1 mm developed. A 12-lead ECG was recorded during exercise and recovery. ST changes were measured 80 ms after the J point. Horizontal or downsloping ST segment depression in any lead of >1 mm, as measured with calipers, was considered a positive response to the stress test.

Of the 350 study patients, 330 performed an exercise test at follow-up. Twenty patients did not perform an exercise test because of unstable angina (n = 14), orthopedic problems (n = 5) and patient refusal (n = 1). No patient used digitalis or showed ECG bundle branch block, rendering the exercise ECG uninterpretable. In patients with an abnormal baseline angiogram, additional ST segment depression ≥1 mm was considered a positive test response.

Restenosis criteria. Sensitivity and specificity for anginal status at follow-up and exercise testing at different cutoff points of continuous quantitative angiographic variables were determined. The angiographic variables were classified as describing the lesion severity at follow-up angiography (static variables—percent diameter stenosis and minimal lumen diameter) or as describing the change in lesion severity at follow-up angiography (dynamic variables—change in percent diameter stenosis and change in minimal lumen diameter). In addition, diagnostic accuracy of six previously proposed definitions of restenosis (9a) was determined: 1) an increase in diameter stenosis of ≥30% by the time of follow-up angiography (National Heart, Lung, and Blood Institute criterion 1 [NHLBI 1]); 2) an immediate postangioplasty diameter stenosis of <50% increasing to ≥70% at follow-up (NHLBI 2); 3) an increase in stenosis severity to within 10% or less of the predilation diameter stenosis at the time of follow-up angiography (NHLBI 3); 4) a loss of ≥50%

Table 1. Baseline Characteristics of the Study Group

Patients (no.)	350
Male	285 (81.4)
Age (yr)	56 ± 9; range 29 to 77
Time to follow-up angiography (days)	172 ± 37
Dilated artery	
LAD	194 (55.4)
RCA	92 (26.3)
LCx	64 (18.3)
History of previous MI	115 (32.9)

Values are expressed as mean value ± 1 SD or number (%) of group. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = myocardial infarction; RCA = right coronary artery.

of the gain achieved at angioplasty (NHLBI 4); 5) increase of lesion severity to >50% diameter stenosis at follow-up; and 6) deterioration in minimal lumen diameter of ≥0.72 mm from immediately postangioplasty to follow-up. The latter criterion is based on the long-term variability of minimal lumen diameter measurements using the CAAS system (0.36 mm). This variability is 1 SD of the mean difference of two measurements of the same lesion filmed at two catheterization sessions an average of 90 days apart (5). This long-term variability reflects the long-term random variation in lesion measurements from coronary angiograms made at different catheterization sessions using the CAAS system (5). The use of 1 SD would include 68.3% of the variability, while the use of 2 SD (2 × 0.36 = 0.72 mm) includes 95.5% of the variability.

Results

Table 1 summarizes the baseline characteristics of the 350 study patients. No differences were found in the proportion of patients with recurrent angina and ST depression at exercise with respect to the vessel dilated (Table 2). The occurence of Q waves in the area supplied by the dilated artery as an indicator of prior transmural infarction (Table 2) was low.

Recurrent angina and quantitative angiography. At follow-up 102 (29%) of 350 patients had recurrent angina. Percent correct classification of recurrence of angina (sensitivity) and percent correct classification of absence of angina at follow-up (specificity) as a function of cutoff points for the different quantitative angiographic variables are given in Figure 1. The point of intersection of the sensitivity and specificity curves represents the cutoff point for which diagnostic accuracy was best. The static variables of minimal lumen diameter at follow-up and percent diameter stenosis at follow-up performed equally well with a sensitivity and specificity slightly >70% at cutoff points of 1.45 mm and 46.5%, respectively. Variables that reflect the change in lesion severity from immediately postangioplasty to follow-up performed only slightly less favorably, with a sensitivity and specificity of just <70% at cutoff points of −0.30 mm for the change in minimal lumen diameter and

Table 2. Ischemia at Follow-Up and Prior Q Wave Infarction by Vessel Type

	Proportion of Patients	p Value
Recurrent angina and		
LAD dilation	28.9% (56 of 194)	
RCA dilation	28.3% (26 of 92)	0.33*
LCx dilation	31.3% (20 of 64)	
ST↓ ≥1 mm at exercise and		
LAD dilation	37.0% (67 of 181)	
RCA dilation	28.7% (25 of 87)	0.91*
LCx dilation	38.7% (24 of 62)	
LAD dilation and		
Q wave in ECG leads V_1 to V_5	10.3% (20 of 194)	
Q wave in ECG leads II, III, aVF	17.0% (33 of 194)	
Q wave in ECG leads V_6, aVL	18.6% (36 of 194)	
RCA dilation and		
Q wave in ECG leads II, III, aVF	3.3% (3 of 92)	
Q wave in ECG leads V_1 to V_5	32.6% (30 of 92)	
Q wave in ECG leads V_6, aVL	28.3% (26 of 92)	
LCx dilation and		
Q wave in ECG leads V_6, aVL	20.3% (13 of 64)	
Q wave in ECG leads V_1 to V_5	23.4% (15 of 64)	
Q wave in ECG leads II, III, aVF	3.1% (2 of 64)	

*Pearson chi-square test. ECG = electrocardiographic; ST↓ = ST segment depression; other abbreviations as in Table 1.

−10% for the change in percent diameter stenosis. To compare the diagnostic accuracy of the different variables, receiver operator characteristic (ROC) curves were constructed (Fig. 2). Quantitative angiographic variables denoting a change in lesion severity are only slightly less accurate than those that denote a static measurement of lesion severity at follow-up.

Positive exercise test and quantitative angiography. The exercise test result was abnormal in 116 patients (35%). Percent correct classification for an abnormal test (sensitivity) and percent correct classification for a normal test (specificity) as a function of cutoff points for the different quantitative angiographic variables are given in Table 3. It is clear that the diagnostic accuracy of exercise testing was lower than for anginal status at follow-up. The optimal combination of sensitivity and specificity was ≈60% for all angiographic variables, with the static variables performing slightly better than the variables of change (Table 3). However, the cutoff points associated with the point of intersection of the sensitivity and specificity curves were similar to those obtained with anginal status. This was 45.5% diameter stenosis at follow-up, 1.46 mm minimal lumen diameter at follow-up, a change of 10% in diameter stenosis and a change of 0.32 mm in minimal lumen diameter. The ROC curves for the different quantitative angiographic variables are shown in Figure 3.

Recurrent angina, positive exercise test result and restenosis criteria in current use. Tables 4 and 5 list the sensitivity, specificity and predictive values for recurrent angina and a positive exercise test result of different previously proposed

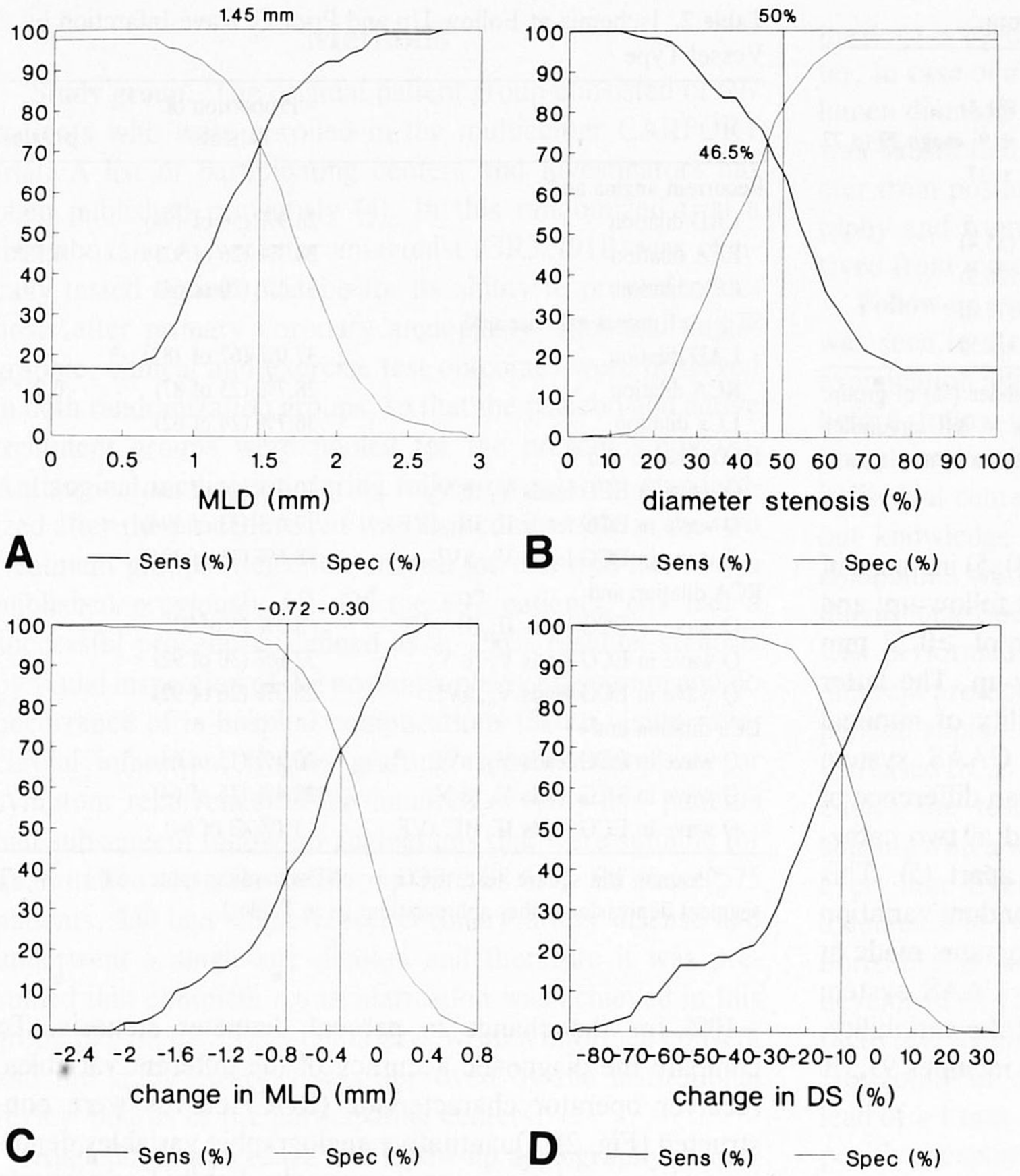
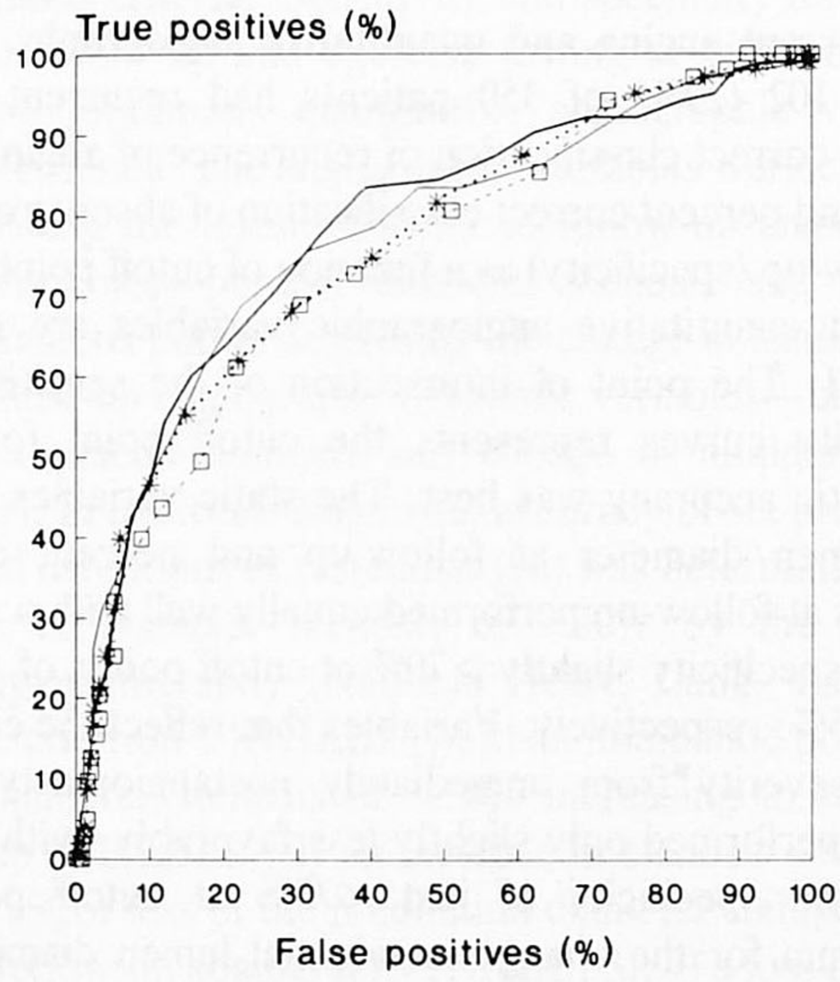


Figure 1. Percent correct classification of recurrence of angina (sensitivity [Sens] %, **darker curve**) and percent correct classification of absence of angina at follow-up (specificity [Spec] %, **lighter curve**) as a function of cutoff points for the different quantitative angiographic variables. The point of intersection of the two curves denotes the cutoff point with the highest diagnostic accuracy. Where appropriate, the 50% diameter stenosis and the ≥0.72-mm loss in minimal lumen diameter [MLD] restenosis criteria were drawn in the figure. **A**, Curves for minimal lumen diameter at follow-up. **B**, Curves for percent diameter stenosis at follow-up. **C**, Curves for change in minimal lumen diameter at follow-up. **D**, Curves for change in percent diameter stenosis (DS) at follow-up.

restenosis criteria. None of the criteria predicted recurrent angina and positive exercise test results with great accuracy. In particular a positive exercise test result was very hard to predict with all angiographic restenosis criteria. Criteria that require a large change (NHLBI 1 and the ≥0.72-mm criterion) and the NHLBI 2 criterion that requires an extraordinary high diameter stenosis at follow-up had a low sensitivity. In fact, the NHLBI 2 criterion is more a predictor of total occlusions because 22 of 26 lesions that fulfilled this criterion were totally occluded at follow-up. Among the 330 patients who underwent exercise testing, 19 of the 22 lesions that fulfilled the NHLBI 2 criterion were totally occluded at follow-up. The NHLBI 3 and 4 criteria and the ≥50% diameter stenosis criterion performed better. The 50% diameter stenosis cutoff point lies close to the optimal cutoff point of 46.5% and is therefore one of the best predictors of recurrent angina or a positive exercise test result whereas the NHLBI 1 criterion (change in diameter stenosis ≥30%) and the ≥0.72-mm criterion are clearly remote from the optimal cutoff points of −10% and −0.32 mm, respectively (Fig. 1, C and D, Table 3).

Figure 2. Receiver operator characteristic curves for comparison of the diagnostic accuracy of anginal status at follow-up for minimal lumen diameter at follow-up (**heavy solid line**), percent diameter stenosis at follow-up (**light solid line**), change in minimal lumen diameter (**dashed line with squares**) and change in percent diameter stenosis (**dotted line with asterisks**).



Diagnostic accuracy of quantitative angiography in large versus small vessels. Coronary arteries taper from proximal to distal. The comparison of proximal with distal coronary

Table 3. Points of Intersection of the Sensitivity and Specificity Curves for the Prediction of Exercise Test Result

Quantitative Angiographic Variable	Intersection Point	Diagnostic Accuracy at Intersection Point* (%)
Minimal lumen diameter (mm)	1.46	58
Diameter stenosis (%)	45.5	58
Change in minimal lumen diameter (mm)	−0.32	58
Change in diameter stenosis (%)	−10	59

*Point at which sensitivity equals specificity. At the point of intersection, diagnostic accuracy is maximal and sensitivity = specificity.

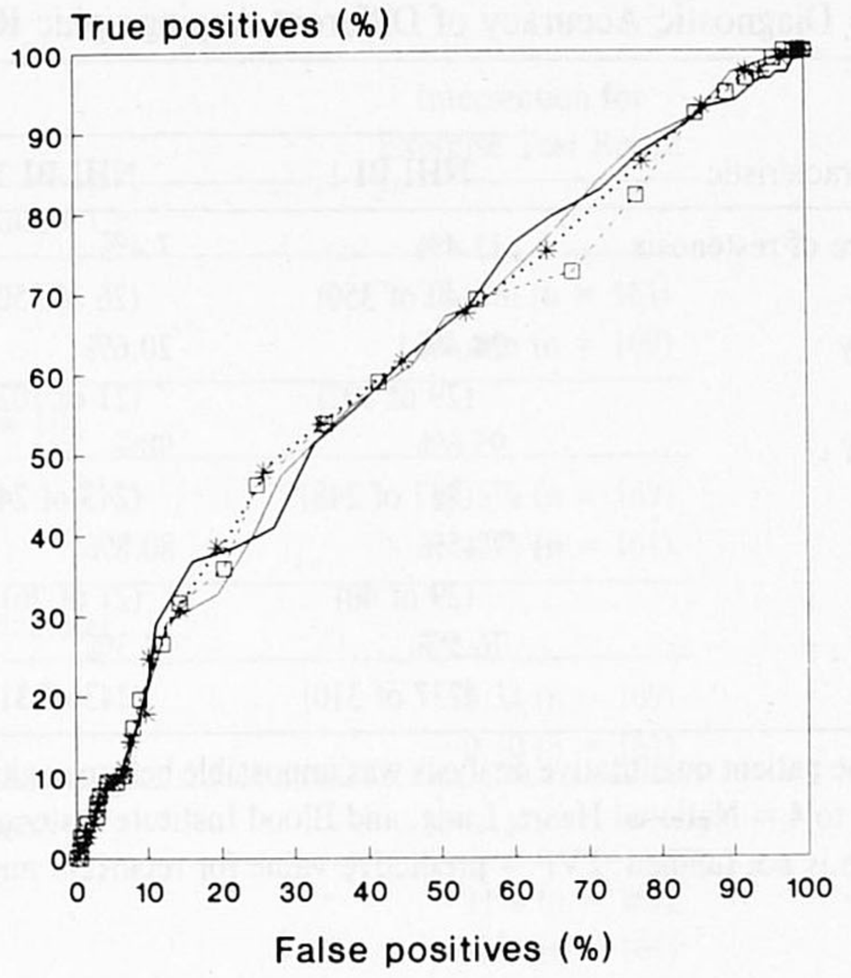


Figure 3. Receiver operator characteristic curves for comparison of the diagnostic accuracy of exercise electrocardiography for minimal lumen diameter at follow-up (**heavy solid line**), percent diameter stenosis at follow-up (**light solid line**), change in minimal lumen diameter (**dashed line with squares**) and change in percent diameter stenosis (**dotted line with asterisks**).

vessels carries the disadvantage of grouping together vessels of different diameter. To study whether the quantitative angiographic values found apply to both large and small vessels we determined the points of intersection of the sensitivity and specificity curves for all four measurements of restenosis. The vessels were therefore divided into two equally large groups according to the reference diameter so that each group contained 50% of the study vessels (Table 6). Large vessels had a reference diameter ≥2.63 mm (n = 176) and small vessels had a reference diameter <2.63 mm. The point of intersection of the sensitivity and specificity curves of the absolute diameter at follow-up was the only quantitative angiographic cutoff point that was different in large vessels as compared with smaller vessels.

Discussion

Patient selection and methodologic considerations. In this study we preferentially studied patients with single-vessel disease and with a single lesion that was successfully dilated. In these patients only restenosis of this lesion can be held responsible for an abnormal ECG response at follow-up exercise testing or recurrent angina, whereas in multivessel disease the responsible lesion is not always easily identifiable. Moreover, coronary angioplasty in multivessel disease will not result in complete revascularization in a considerable number of cases (10).

With conventional exercise protocols, ECG leads and ECG criteria, exercise testing is characterized by a high specificity and a moderate sensitivity (11). Furthermore, its sensitivity increases with the extent of coronary artery disease, which implies a low sensitivity in patients with single-vessel disease (12–14). This explains the low predictive accuracy found in our population of patients with single-vessel disease for the different restenosis criteria. These findings are comparable with the findings of Bengtson et al. (15), who found a sensitivity of 32% and a specificity of 79% for a positive exercise ECG.

It is known that diagnostic accuracy for restenosis of recurrent angina is better than for ST segment change (15,16). From the data of Bengtson et al. (15), a sensitivity for recurrent angina of 59% and a specificity of 73% can be calculated. They applied the 50% diameter criterion for restenosis. Zaidi et al. (17) reported a sensitivity of 70% and a specificity of 66% for recurrence angina as a test for restenosis. Although the predictive accuracy of quantitative angiographic variables was generally poor in the present study, it is remarkable that the points of intersection of the sensitivity and specificity curves were similar for two different markers of myocardial ischemia.

Angioplasty of the left anterior descending artery made up 55.4% of all procedures in this study. It might be argued that the large mass of myocardium supplied by this artery, which is potentially ischemic in case of severe renarrowing, would render the findings of this study applicable only to left anterior descending artery lesions. However, no differences were found in the proportion of patients with recurrent angina and ST depression at exercise with respect to the vessel dilated (Table 2). Prior myocardial infarction is known to falsely increase the accuracy of exercise testing (18). However, the occurrence of Q waves in the area supplied by the dilated artery (Table 2) was low, indicating only a small possible influence on our findings.

Angiographic restenosis and functional status. Restenosis after a successful angioplasty procedure is now viewed as a fibroproliferative repair process in response to traumatic injury to the vessel wall (19,20). We recently showed that lumen narrowing after angioplasty occurs to a certain extent in all dilated lesions (21) and that angiographic restenosis is the tail end of a normally distributed phenomenon. The restenosis rate is then dependent on the cutoff criterion applied. Generally two types of angiographic restenosis criteria have been developed: criteria that denote the change

Table 4. Diagnostic Accuracy of Different Angiographic Restenosis Criteria for Patients With Recurrent Angina

Characteristic	Criterion					
	NHLBI 1	NHLBI 2	NHLBI 3*	NHLBI 4*	≥50% DS	≥0.72 mm
Prevalence of restenosis	11.4% (40 of 350)	7.4% (26 of 350)	31.2% (109 of 349)	34.7% (121 of 349)	31.7% (111 of 350)	17.7% (62 of 350)
Sensitivity	28.4% (29 of 102)	20.6% (21 of 102)	60.8% (62 of 102)	64.7% (66 of 102)	63.7% (65 of 102)	39.2% (40 of 102)
Specificity	95.6% (237 of 248)	98% (243 of 248)	81% (200 of 247)	77.7% (192 of 247)	81.5% (202 of 248)	91.1% (226 of 248)
PVP	72.5% (29 of 40)	80.8% (21 of 26)	56.9% (62 of 109)	54.5% (66 of 121)	58.6% (65 of 111)	64.5% (40 of 62)
PVN	76.5% (237 of 310)	77.3% (243 of 314)	83.3% (200 of 240)	84.2% (192 of 228)	84.5% (202 of 239)	78.5% (226 of 288)

*In one patient quantitative analysis was impossible before angioplasty; therefore, these criteria could not be assessed in this patient. DS = diameter stenosis; NHLBI 1 to 4 = National Heart, Lung, and Blood Institute restenosis criteria (see Methods for definitions); PVN = predictive value for no angina at follow-up if criterion is not fulfilled; PVP = predictive value for recurrent angina at follow-up if criterion is fulfilled.

in stenosis severity at follow-up angiography (e.g., the ≥0.72-mm change criterion) and criteria that assess stenosis severity at follow-up angiography (e.g., the >50% diameter stenosis at follow-up criterion). From a functional point of view restenosis can be detected by recurrence of angina and by several noninvasive tests. These tests are aimed at detecting myocardial ischemia due to a flow-limiting stenosis in an epicardial artery and give no information on the magnitude of the lumen-narrowing process in the individual lesion. Angiographic restenosis criteria that give a static assessment of lesion severity at follow-up have the disadvantage of preselecting lesions with a marginal angioplasty result (1). This means that these lesions have to undergo only a small deterioration to cross the cutoff point and be classified as "restenosed." Classically the 50% diameter stenosis criterion is applied to classify lesions or patients as "restenosed" at follow-up angiography after angioplasty. This definition is historically based on the physiologic concept of coronary flow reserve introduced by Gould and others (22) in 1974 and is taken because it represents the approximate value in animals with normal coronary arteries at which blunting of the hyperemic response occurs. Although the 50% diameter stenosis criterion is attractive because it links the angiographic appearance of a lesion with the clinical situation of the patient, it tells us nothing about the dynamic behavior of the restenosis process. Our findings underscore the significance of the 50% diameter stenosis criterion because the optimal cutoff point for prediction of functional status 6 months after coronary angioplasty was found to be close to this value (46.5% diameter stenosis). However, diagnostic accuracy of the *absolute* stenosis diameter at 6 month follow-up was similar to percent diameter stenosis (Fig. 2 and 3) with a point of intersection of the sensitivity and specificity curves for both anginal status and exercise test results at approximately 1.45 mm. This observation indicates that an absolute measure of stenosis severity is equally predictive of clinical status after angioplasty as a relative measurement. These values correspond well with the findings of Wilson et al. (23). They found that coronary flow reserve dropped below 3.5 (the lower threshold of normal) at a minimal cross-sectional area of 1.5 mm^2 and a percent area stenosis of 75%, which corresponds to a mini-

Table 5. Diagnostic Accuracy of Different Angiographic Restenosis Criteria for Patients With a Positive Bicycle Ergometry Response at Follow-Up

Characteristic	Criterion					
	NHLBI 1	NHLBI 2	NHLBI 3*	NHLBI 4*	≥50% DS	≥0.72 mm
Prevalence of restenosis	11.2% (37 of 330)	6.7% (22 of 330)	30.7% (101 of 329)	34.7% (114 of 329)	31.2% (103 of 330)	17% (56 of 330)
Sensitivity	14.7% (17 of 116)	9.5% (11 of 116)	37.9% (44 of 116)	46.5% (54 of 116)	41.4% (48 of 116)	26.7% (31 of 116)
Specificity	90.7% (194 of 214)	94.9% (203 of 214)	73.2% (156 of 213)	71.8% (153 of 213)	74.3% (159 of 214)	88.3% (189 of 214)
PVP	45.9% (17 of 37)	50% (11 of 22)	43.6% (44 of 101)	47.4% (54 of 114)	46.6% (48 of 103)	55.4% (31 of 56)
PVN	66.2% (194 of 293)	65.9% (203 of 308)	68.4% (156 of 228)	71.2% (153 of 215)	70% (159 of 227)	69% (189 of 274)

*In one patient quantitative analysis was impossible before angioplasty; therefore, these criteria could not be assessed in this patient. Abbreviations as in Table 4.

Table 6. Point of Intersection for Small and Large Vessels

Reference Diameter	Intersection for Anginal Status	Intersection for Exercise Test Result
	Minimal Lumen Diameter at Follow-Up	
<2.63 mm	1.38 mm (n = 176)	1.37 mm (n = 161)
≥2.63 mm	1.58 mm (n = 174)	1.57 mm (n = 169)
	Diameter Stenosis at Follow-Up	
<2.63 mm	47.5% (n = 176)	44.5% (n = 169)
≥2.63 mm	46% (n = 174)	44% (n = 161)
	Change in Minimal Lumen Diameter	
<2.63 mm	−0.33 mm (n = 176)	−0.34 (n = 169)
≥2.63 mm	−0.27 mm (n = 174)	−0.30 (n = 161)
	Change in Diameter Stenosis	
<2.63 mm	−11% (n = 176)	−11% (n = 169)
≥2.63 mm	−9% (n = 174)	−9% (n = 161)

mal lumen diameter of 1.4 mm and a percent diameter stenosis of 50%, respectively. Wijns et al. (24) demonstrated a steep increase in pressure drop over left anterior descending artery stenoses once a critical value of minimal cross-sectional area of 2.5 mm^2 was reached. This corresponds to a minimal lumen diameter of 1.78 mm. The pressure measurements were made with a dilation catheter across the stenosis (cross-sectional area of catheter = 0.64 mm^2). If this value is subtracted from the 2.5-mm^2 value, a minimal lumen diameter value of 1.54 mm emerges, which is close to the 1.45 mm found in the present study.

An approach that more closely reflects the magnitude of the reactive intimal hyperplasia after angioplasty is applying criteria that describe the change in lesion severity at follow-up angiography. The major critique of this type of criterion is that it might disregard the functional significance of a lesion at follow-up. For instance a lesion with a postangioplasty percent diameter stenosis in the range of 0 to 15% can undergo a large deterioration and still not be flow limiting. However, our study shows not only that the static variables of minimal lumen diameter and percent diameter stenosis perform equally well in predicting clinical significance of a lesion 6 months after successful coronary angioplasty, but also that the variables of change in lumen diameter and change in percent diameter stenosis were only slightly less accurate in predicting the clinical significance of the lesions (Fig. 2 and 3). Therefore, variables of change, apart from their usefulness in reflecting the magnitude of the reactive hyperplasia, also reflect nearly to the same extent as the static variables, the clinical significance of the lesion at follow-up. The optimal cutoff point for the variables of change was −0.30 mm for the change in lumen diameter and −10% for change in percent diameter stenosis with nearly equal diagnostic accuracies showing that absolute change in lesion severity (in mm) and relative change in lesion severity (in percent) perform equally well in the prediction of recurrent angina or a positive exercise ECG response 6 months after coronary angioplasty.

Limitations of the study. First, more sophisticated invasive and noninvasive methods are available for the assessment of the functional significance of a coronary stenosis. It is known that exercise thallium scintigraphy has a higher diagnostic accuracy than does ECG exercise testing (25). The present data originate from a multicenter trial and therefore it is logistically difficult to standardize the methodology of radionuclide exercise tests or flow reserve measurements in all participating centers. Exercise ECG testing on the other hand is inexpensive and safe, and identical exercise protocols can be easily implemented in the participating centers. As proposed by Popma et al. (26), paired stress tests (shortly after angioplasty and at 6 months follow up) should ideally be obtained, otherwise the interpretation of an ischemic exercise test at follow-up may be more difficult, especially in patients with multivessel coronary artery disease. Our study group consisted of patients with single-vessel disease in whom complete revascularization was achieved. However, the absence of myocardial ischemia at hospital discharge after angioplasty was not objectively confirmed by exercise testing. The diagnostic accuracy of quantitative angiographic variables for the prediction of recurrent angina and an abnormal ECG response at exercise was not very high. Nevertheless, the absolute values of sensitivity and specificity were not crucial to this study, but rather the point of intersection of the sensitivity and specificity curves. Anginal medication was not standardized in this study. This factor might have influenced the assessment of functional status; however, an attempt was made to withdraw antianginal medication at least 24 h before exercise testing. Finally, all angiograms were preceded by an intracoronary dose of nitrates and not all patients were using vasodilator drugs at the time of exercise testing. This factor might have shifted the points of intersection toward a higher

minimal lumen diameter and a lower percent diameter stenosis.

Conclusions. The large number of patients studied and the fact that the same optimal values for diagnostic accuracy of the various quantitative angiographic variables were obtained for the prediction of two different markers of ischemia (anginal status and ST depression at exercise) suggest that these values reflect the lesion severity or increase in lesion severity in major epicardial vessels at which coronary flow reserve is unable to meet myocardial demands. Relative measurements (percent diameter stenosis) and absolute measurements (minimal lumen diameter) were found to be equally predictive of ischemia. Because the minimal lumen diameter is the most unambiguous measurement of lesion severity (independent of an arbitrary normal part of the artery), this measure can be a more reliable surrogate for clinical outcome than the classic percent diameter stenosis measurement in the many restenosis prevention trials with drugs and new devices currently underway or in the design phase.

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