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STRESS TESTING

Quantitative Coronary Angiography in the Estimation of the Functional Significance of Coronary Stenosis: Correlations With Dobutamine-Atropine Stress Test

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Objectives. **The purpose of this study was to determine the predictive value of quantitative coronary angiography in the assessment of the functional significance of coronary stenosis as judged from the development of left ventricular wall motion abnormalities during dobutamine-atropine stress echocardiography.**

Background. **Coronary angiography is the reference method for assessment of the accuracy of noninvasive diagnostic imaging techniques to detect the presence of significant coronary stenosis. However, use of arbitrary cutoff criteria for the interpretation of angiographic data may considerably influence the true diagnostic accuracy of the technique investigated.**

Methods. **Thirty-four patients without previous myocardial infarction and with single-vessel coronary stenosis were studied with both quantitative angiography and dobutamine-atropine stress echocardiography. Two different techniques of quantitative angiographic analysis—edge detection and videodensitometry—were used for measurement of minimal lumen diameter, percent diameter stenosis and percent area stenosis. Two-dimensional echocardiographic images were collected during incremental doses of intravenous dobutamine and later analyzed using a 16-segment left ventricular model. Angiographic cutoff criteria were derived from receiver-operating curves to define the functional significance of coronary stenosis on the basis of dobutamine-atropine stress echocardiography.**

Results. **The angiographic cutoff values with the best predictive value for the development of left ventricular wall motion abnormalities during dobutamine-atropine stress echocardiography were minimal lumen diameter of 1.07 mm, percent diameter stenosis of 52% and percent area stenosis of 75%. Minimal lumen diameter was found to have the best predictive value for a positive dobutamine stress test (odds ratio 51, sensitivity 94%, specificity 75%).**

Conclusions. **Automated quantitative angiographic measurement of minimal lumen diameter is a practical and useful index for determining both the anatomic and functional significance of coronary stenosis, and a value of 1.07 mm is the best predictor for a positive dobutamine stress test.**

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Establishing the functional significance of coronary stenosis detected by contrast angiography is a clinical challenge, especially in the case of intermediate stenotic lesions. The traditional criteria for determining the presence of functionally significant disease, a 50% reduction in lumen diameter by visual estimation, suffers from considerable interobserver and intraobserver variability (1–3), making this criterion unreliable in the estimation of the functional impact of lumen obstructions (3). It is in the range of mild to moderate stenoses (30% to 60% diameter stenosis) that the discrepancy between visual estimates and objective measurements of lumen dimensions is most marked (4,5). Computerized quantitative coronary angiography reduces the latter source of error and provides objective measurements of lumen dimensions, but the physiologic significance of a given coronary stenosis remains unclear. Because of the use of arbitrary cutoff criteria in previous studies addressing this problem, and in which coronary angiographic estimates of severity were compared with other imaging, objective indexes are lacking.

Recently, dobutamine stress echocardiography has been introduced as a safe and reproducible technique for the diagnosis of coronary artery disease (6–13). Several studies have indicated good correlation between the development of wall motion abnormalities during stress echocardiography and the severity of coronary stenosis (6–15). However, these studies have limitations because either visual interpretation

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of the angiogram was performed (6,7,14) or arbitrary cutoff points (13) for quantitative angiographic data were used.

The goal of this study was to investigate which quantitative angiographic variables of stenosis severity best correlate with the development of ischemia-induced wall motion abnormalities during dobutamine-atropine stress echocardiography. Angiographic cutoff criteria were derived from receiver-operating curves to obtain objective criteria for assessment of functional significance of stenosis severity.

Methods

Study patients. The study patients included 34 consecutive patients referred from the catheterization laboratory, with a single-vessel coronary stenosis judged to have ≥30% diameter stenosis by visual assessment. The coronary angiogram was performed within 2 weeks before the performance of dobutamine-atropine stress echocardiography. The stenosis was located in the left anterior descending coronary artery in 26 patients, left circumflex coronary artery in 3 patients and right coronary artery in 5 patients. Mean age was 61.3 ± 12.6 years (range 32 to 79). There were 21 (62%) men and 13 (38%) women. Patients with unstable angina, previous myocardial infarction and left bundle branch block were excluded. Patients were receiving antianginal medication, consisting of beta-adrenergic blocking agents (24 patients), either alone or in combination with nitrates, or calcium-channel blocking agents, or both, that was not discontinued before the study.

Dobutamine-atropine stress test. The protocol used at the Thoraxcenter in the performance of dobutamine-atropine stress echocardiography has been described in detail elsewhere (16). Briefly, two-dimensional precordial echocardiography was performed at rest and during incremental doses of dobutamine. After a baseline 12-lead electrocardiogram (ECG), dobutamine was infused through an antecubital vein starting at a dose of 10 μg/kg body weight per min for 3 min and increasing by 10 μg/kg per min every 3 min to a maximum of 40 μg/kg per min (stage 4). This was continued for 6 min in the absence of an ischemic response. In patients not achieving 85% of maximal predicted heart rate, atropine (0.25 mg) was given intravenously at the end of stage 4 and repeated to a maximum of 1 mg with the continuation of dobutamine for a further 5 min if necessary to achieve the previously mentioned target heart rate. The infusion of dobutamine was stopped if the patient developed marked new wall motion abnormalities, ST segment depression >0.2 mV 80 ms after the J point, ST segment elevation, typical angina, significant arrhythmias, a decrease in systolic blood pressure >40 mm Hg from rest level or any complication considered to be related to the stress test.

Standard apical and parasternal views were recorded in a closed cine loop quad-screen format on super-VHS videotape, facilitating the comparison of rest and stress images. During the analysis of the images, the left ventricle was divided into 16 segments (17), and each segment was scored using a four-point scale: 1 = normal wall motion and thickening; 2 = hypokinesia; 3 = akinesia (absence of systolic wall motion and thickening); 4 = dyskinesia (systolic outward wall motion with thinning).

Images were reviewed by two experienced investigators who were unaware of the clinical and angiographic data. Agreement between the two observers was required for the classification of wall motion abnormalities. In cases of disagreement, the opinion of a third investigator was considered. An ischemic response was defined as a stress-induced new wall motion abnormality or a worsening of wall motion abnormality at rest.

The location of wall motion abnormalities was correlated with coronary arterial distribution by the same methodology as previously described by Segar et al. (13), after a modification of the scheme of Bourdillon et al. (17). The apical lateral and apical inferior segments were considered to be areas of overlap. The apical lateral segment was considered to be part of the left anterior descending coronary artery territories in association with additional septal or anterior wall motion abnormalities. The same segment was considered to be part of the left circumflex coronary artery distribution in association with posterior or posterolateral wall motion abnormalities. The apical inferior segment was related to the right coronary artery system if there were additional inferior wall motion abnormalities and to the left anterior descending coronary artery region in the presence of anterior or anteroseptal wall motion abnormalities.

Quantitative coronary angiography. All 35-mm films were analyzed using the Cardiovascular Angiography Analysis System II (CAAS II, Pie Medical). The automated edge detection and videodensitometric techniques of this system have been validated and described in detail elsewhere (18–22). All measurements were performed from end-diastolic frames with optimal vessel opacification.

Edge detection. A region of interest of 512 × 512 pixels was selected and digitized using a high fidelity charge-coupled device video camera. The lumen edges were detected on the basis of the weighted sum of the first and second derivative function of the brightness profile of each scan line perpendicular to the vessel centerline. The vessel diameter function was determined by computing the shortest distance between the right and left contours. Calibration of these measurements to absolute values was achieved by using the catheter tip as a scaling device. A computer-derived estimation of the original arterial dimension at the site of obstruction was used to calculate the interpolated reference diameter. This technique is based on a computer-derived estimation of the original values over the analyzed region. The calculation is based on a first-degree polynomial computed through the diameter values of the proximal and distal portions of the arterial segment, followed by a translation to the 80th percentile level.

Videodensitometry. Densitometry is based on the approximate linear regression that exists between the optical density of a contrast-enhanced lumen and its absolute di-

Table 1. Results of Dobutamine Stress Test in Study Groups 1 and 2

	Group 1 (n = 18)	Group 2 (n = 16)
% Maximal heart rate	82 ± 14	69 ± 17*
Stress angina	6 (18%)	5 (15%)
Ischemic ST segment deviation	5 (15%)	3 (9%)
Atropine	8 (53%)	7 (47%)

*p < 0.05. Data presented are mean value ± SD or number (%) of patients.

mensions. To follow this approach, the brightness of each scan line perpendicular to the vessel centerline was transformed into an absorption profile using a simple logarithmic transfer function to correct for the Lambert-Beer law. The background contribution was estimated by computing the linear regression line through the background pixels located left and right of the detected lumen contours. By subtracting this background portion from the absorption profile of the vessel, a net cross-sectional absorption profile was calculated. A cross-sectional area function of the analyzed segment was obtained by repeating this process with all scan lines. An interpolated reference area was calculated from the reference diameter assuming a circular cross section. The cross-sectional area at the narrowest point was identified and expressed in mm^2.

Data analysis. All continuous variables are expressed as mean value ± SD. The two-tailed Student *t* test was used for analysis of continuous data. The chi-square test and Fisher exact test were used to compare differences between proportions. The independent correlation of the angiographic variables to the percent of the maximal age-predicted heart rate was determined by logistic regression analysis. Angiographic variables were entered as categoric variables by use of their respective cutoff values. These values were achieved by determining for each variable the point of the maximal sum of sensitivity and specificity, when the sensitivity is equal to or greater than the specificity. Furthermore, receiver-operator characteristics curve analysis as an objective method for determining the value of the various angiographic variables in the prediction of an abnormal dobutamine stress test was applied. This technique is independent of definitions of cutoff values. The sensitivity (true positive) is plotted against 1 − Specificity (true negative) during the whole range of measurements of a specific variable. Odds ratio and 95% confidence intervals were calculated for comparison of the relative predictive power of the best cutoff value for each angiographically determined variable. A p value < 0.05 was considered statistically significant. The statistical package used was SAS, release 6.04 (SAS Institute).

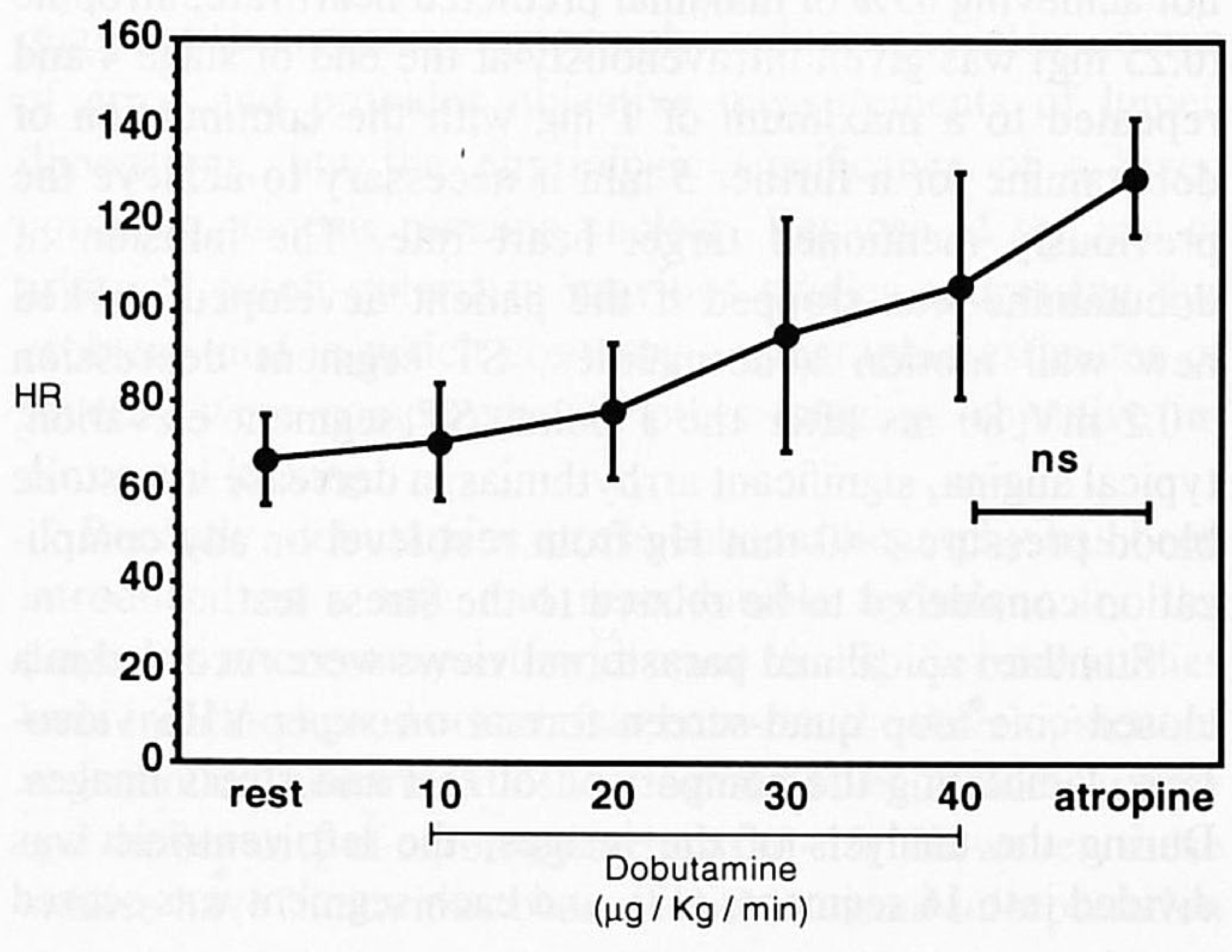
Results

Results of dobutamine-atropine stress test. Dobutamine-atropine stress echocardiography was positive in 18 patients. There were no significant differences in age, gender or affected coronary artery between patients with a positive (group 1) or negative (group 2) test. Beta-blockers were part of the antianginal therapy in 24 patients (70%). Of these, 10 patients (4%) developed a positive dobutamine stress test compared with 14 (58%) with a negative test (p = NS).

Table 1 summarizes the results of the dobutamine-atropine stress test. The percent of the maximal age-predicted heart rate achieved was noted to be significantly higher (82 ± 14) in group 1 than in group 2 (69 ± 17) ($p < 0.05$) and in patients without beta-blocker therapy (87 ± 9 vs. 72 ± 17, $p < 0.05$). Atropine was added in 15 patients (12 were receiving beta-blocker therapy). However, because the presence and severity of the disease is the main determinant of a positive test, the achievement of the target heart rate was not found by logistic regression analysis to be an independent predictor of a positive stress test. In Figure 1, the evolution of the heart rate during the test is shown. Although the maximal heart rate when atropine was added was higher, it did not change the sensitivity of the test. It was also evident that patients taking beta-blockers frequently need atropine at the end of the test to achieve the target heart rate. During the test, angina occurred in 11 patients (32%), with equal distribution in the two groups (6 patients in group 1, 5 patients in group 2, p = NS). An ischemic ECG response during stress testing occurred in eight patients (24%), and again there were no significant differences between the two groups (five patients in group 1, three patients in group 2, p = NS).

Results of quantitative angiography. For the entire group, quantitative coronary angiography revealed a mean percent diameter stenosis of 56 ± 20% (range 11% to 100% [four patients had total occlusion]), mean percent area stenosis of 74 ± 20% (range 24% to 100%), mean minimal lumen diameter of 1.01 ± 0.59 mm (range 0 to 2.84 mm) and mean

Figure 1. Evolution of heart rate (HR) during dobutamine infusion and atropine administration. Clearly seen is the steep increase in heart rate with the addition of atropine, although the difference in maximal heart rate between patients who did and did not receive atropine was not statistically significant.



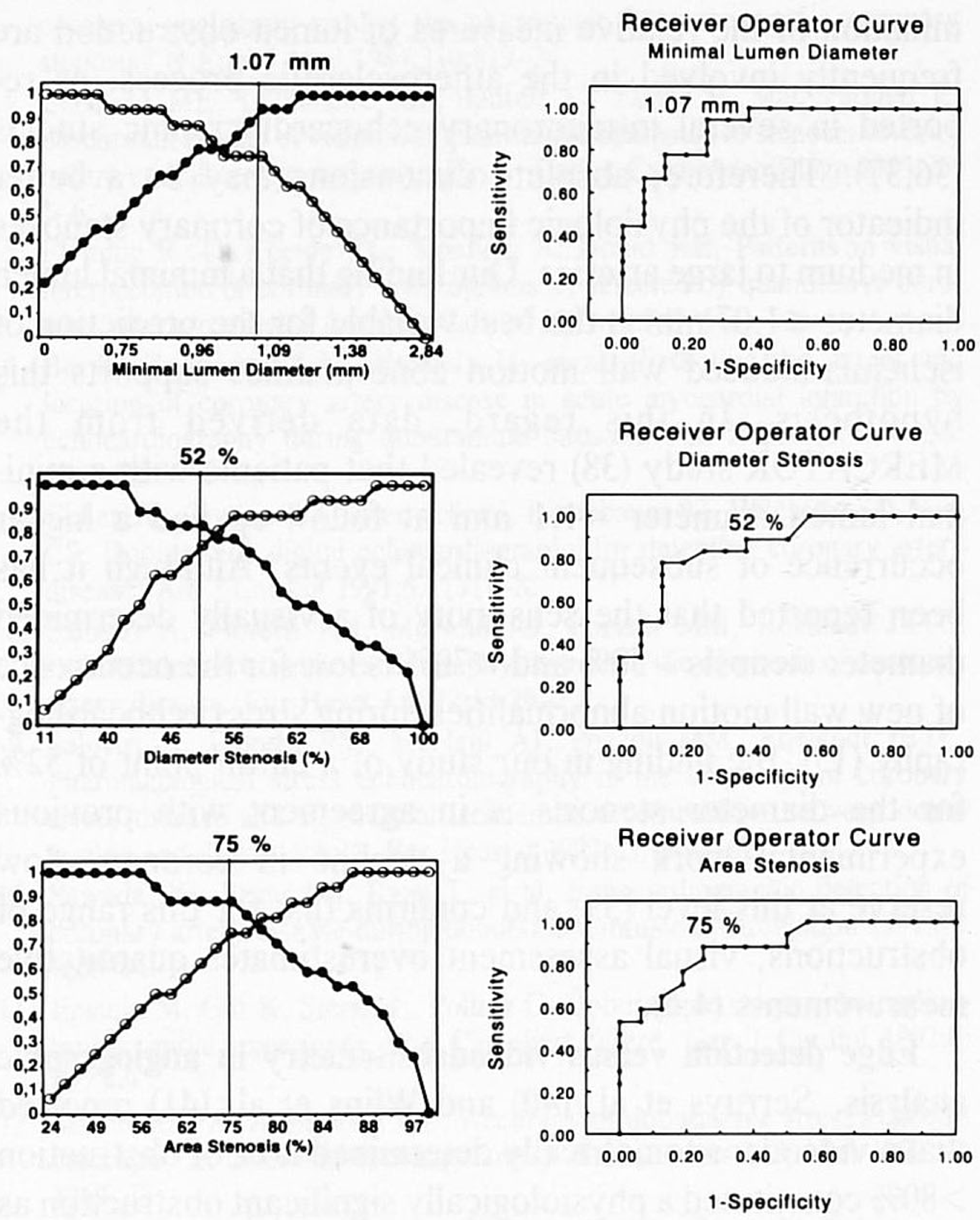


Figure 2. Relation between the sensitivity and specificity of the dobutamine-atropine stress test and the receiver-operator curves for each of the angiographic indexes as a function of stenosis severity. **Left**, Variation in sensitivity (**solid circles**) and specificity (**open circles**) are presented as a function of cutoff points for the different quantitative angiographic variables. **Right**, Corresponding receiver-operator curves for the angiographic variables.

reference diameter of 2.41 ± 0.52 mm (range 1.64 to 4.07 mm).

Figure 2 shows the relation between the sensitivity and specificity of the dobutamine-atropine stress test and their receiver-operator characteristics curves for each of the angiographic indexes as a function of stenosis severity. For clinical purposes, a cut point is often selected to permit computation of sensitivity and specificity, variables that are widely used and understood in the published reports (23). There are two commonly used schemes for selecting cut points in this setting. The first involves the choice of a convenient but arbitrary point, such as 50% diameter stenosis. The second uses the intersect of the sensitivity and specificity curves as the cut point (24). In the present study an alternative approach was used on the basis of receiver-operator characteristics curves. We selected the point at which the sum of the sensitivity and specificity, when the sensitivity is equal to or greater than the specificity, reaches a maximum. Because this point takes into account the shape of the two curves near the point of interception (Fig. 2), it was hoped that this technique would provide better diagnostic accuracy. As an example, in Figure 2 if we select the interception of the sensitivity and specificity curves, the sum will be 159 points (sensitivity 78 + specificity 81). Using our approach, the sum of the sensitivity and specificity will be 169 (sensitivity 94 + specificity 75).

All the quantitative angiographic variables revealed a high sensitivity (range 82% to 94%) for the identification of ischemia-induced wall motion abnormalities. Although all the angiographic variables had the same specificity (75%), minimal lumen diameter had the highest sensitivity (94%). Because patients with normal coronary arteries were not included in the study, the specificity value is probably underestimated.

Table 2 summarizes the relation of different cutoff points to the outcome of the stress test. Minimal lumen diameter has a predictive value that is considerably larger (odds ratio 51) than the commonly used variables of relative obstruction (odds ratio of 15 and 23 for percent diameter and percent area stenosis, respectively).

Discussion

Dobutamine stress echocardiography. The use of dobutamine stress echocardiography in the assessment of myocardial ischemia offers advantages over the traditional nuclear techniques, including lower cost, less time, no radiation exposure and greater availability, that justify its growing application in clinical practice (6–10,12,13). Because wall motion abnormalities are an early and specific indicator of myocardial ischemia, dobutamine stress echocardiography is potentially superior to stress scintigraphy, particularly in patients with mild to moderate stenoses, where transient perfusion defects result from a maldistribution of coronary flow and do not necessarily reflect "true" myocardial ischemia. In addition, single-photon emission computed tomographic (SPECT) myocardial scintigraphy is

Table 2. Quantitative Angiographic Results According to Cutoff Values

Angiographic Cutoff Values	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Odds Ratio
MLD ≤1.07 mm	94 (84–100)	75 (54–96)	81	92	51 (4–1,929)
A Ste ≥75%	88 (73–100)	75 (54–96)	79	86	23 (2–242)
D Ste ≥52%	83 (66–100)	75 (54–96)	79	80	15 (2–123)

Numbers in parentheses are 95% confidence intervals. A Ste = area stenosis; D Ste = diameter stenosis; MLD = minimal lumen diameter.

associated with a lower specificity compared with dobutamine stress echocardiography in patients with a single-vessel coronary stenosis (25,26).

In the study patients the incidence of chest pain and ischemic ECG response during dobutamine echocardiography was low (32% and 24%, respectively), without relation to the outcome of the echocardiographic stress test. This is not surprising, because in previous studies the sensitivity and specificity of stress-induced ECG changes in single-vessel disease were also relatively low (27–30). The finding of a significant higher heart rate in patients who developed wall motion abnormalities during dobutamine stress echocardiography underlines the importance of chronotropism as an additional mechanism to increase inotropism to induce ischemia. This is in agreement with previous experimental and clinical data (16,31,32).

Previous studies. In previous studies, quantitative angiographic measurements of stenosis severity correlated well with the outcome of stress echocardiography (13,15). In a group of 25 patients with single-vessel disease, Ryan et al. (14), using the criterion of >50% visually determined percent diameter stenosis, found a sensitivity of 76% for exercise echocardiography. Sheikh et al. (15) studied 34 patients with single-vessel obstruction and reported that all patients with >75% diameter stenosis by visual assessment developed wall motion abnormalities during exercise echocardiography. However, only 50% of the same patients had an abnormal test if the angiographic cutoff criterion was lowered to 50% diameter stenosis. In a subgroup of 30 patients with normal left ventricular function at rest and single or multivessel disease, Segar et al. (13) described high sensitivity (90%) of the dobutamine stress test to detect significant coronary disease using a diameter stenosis >50% by quantitative angiography. Several investigators (8,10,12,16) using the same approach reported a wide variation in the sensitivity values for the detection of significant lumen reduction. All these studies, however, relied on arbitrary cutoff points for the determination of significant stenosis, and few evaluated (13,15) absolute variables of lumen obstruction. The high sensitivity and specificity noted for minimal lumen diameter in our study (94% and 75%, respectively), although using a different approach, are in accordance with Segar et al. (13), who reported a high sensitivity of the dobutamine stress test in the identification of coronary stenoses using a cutoff criterion of 1.0 mm for minimal lumen diameter; however, in their study an attempt to determine the best cutoff point was not reported.

Relative versus absolute measurements of coronary stenosis. It is known that in the setting of diffuse coronary artery disease, relative variables of lumen narrowing may underestimate the functional impact of stenosis severity (33–35). In this study, only patients with a single discrete stenosis were included. Therefore it is of greater significance that minimal lumen diameter was found to be the best predictor of an abnormal stress test. However, even in the presence of focal disease, angiographically normal segments used in the determination of the relative measures of lumen obstruction are frequently involved in the atherosclerotic process, as reported in several intracoronary echocardiographic studies (36,37). Therefore, absolute dimensions may be a better indicator of the physiologic importance of coronary stenoses in medium to large arteries. Our finding that a minimal lumen diameter ≤1.07 mm is the best variable for the prediction of ischemia-induced wall motion abnormalities supports this hypothesis. In this regard, data derived from the MERCATOR study (38) revealed that patients with a minimal lumen diameter <1.1 mm at follow-up had a higher occurrence of subsequent clinical events. Although it has been reported that the sensitivity of a visually determined diameter stenosis >50% and <70% is low for the occurrence of new wall motion abnormalities during stress echocardiography (15), the finding in our study of a cutoff point of 52% for the diameter stenosis is in agreement with previous experimental work showing a decline in coronary flow reserve at this level (39) and confirms that for this range of obstructions, visual assessment overestimates quantitative measurements (4,5).

Edge detection versus videodensitometry in angiographic analysis. Serruys et al. (40) and Wijns et al. (41) reported that a videodensitometrically determined area of obstruction >80% constituted a physiologically significant obstruction as assessed by exercise-redistribution thallium scintigraphy, and these data agree with our criterion of a 75% reduction in cross-sectional area for the prediction of ischemia-induced wall motion abnormalities. Videodensitometric determination of percent area obstruction is theoretically independent of the geometric shape of the lumen obstruction, having the potential to overcome limitations related to edge detection techniques when using a single projection. In our study an average of two projections was used to determine the different angiographic variables, and situations where the occurrence of a complex lumen shape were not included in the analysis (e.g., postangioplasty, unstable angina); therefore, there was no clear advantage of the densitometrically determined percent area stenosis over percent diameter stenosis.

Conclusions. Quantitative angiography provides an objective assessment of the functional significance of coronary stenoses as determined by dobutamine stress echocardiography. Although relative measurements of lumen obstruction are predictive of an abnormal stress echocardiogram, minimal lumen diameter appears to be the optimal variable in the determination of the physiologic significance of coronary stenoses in medium to large arteries.

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