What Percent Luminal Stenosis Should Be Used to Define Angiographic Coronary Artery Disease for Noninvasive Test Evaluation?

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Background: There has been controversy over what is the best angiographic luminal dimension criterion associated with ischemia for evaluating diagnostic tests. If one assumes that ST-segment depression or scores are indicators of ischemia, then whatever angiographic criteria best discriminates those with ischemic and nonischemic responses would be the best angiographic marker for ischemia. To study this, we calculated the area under the ROC curves for ST depression and scores at different angiographic cut-points in order to determine the best angiographic cut-point for defining ischemia-producing coronary disease.

Methods: Twelve hundred and seventy-six consecutive males without prior MI with a mean age of 59 ± 11 years who had undergone exercise testing and coronary angiography were analyzed in this study. We calculated the number of patients of this population that would be considered to have coronary artery disease at different cut-points for angiographic luminal stenosis. For example, 59% of the patients had significant CAD when disease was defined as 50% or greater coronary lumen stenosis of any coronary vessel while 49% of the patients had significant CAD when disease was defined as 70% or greater coronary lumen stenosis. Cut-points were considered between 40 to 100% coronary lumen stenosis. ROC analysis was then performed comparing ST depression and treadmill scores at each of these cut-points.

Results: The cut-point for coronary lumen stenosis that returned the highest AUC for ST depression and scores was between 70 and 80% coronary luminal stenosis. However, the difference between the 50% and 75% luminal stenosis criteria was minimal.

Conclusion: It appears that the best cut-point for defining significant angiographic disease when evaluating diagnostic tests of ischemia is 75% or greater coronary luminal stenosis.

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Since coronary angiography was introduced in 1957,[1] there has been controversy over the angiographic definition of significant coronary artery disease. In 1966, a study by Proudfit et al. revealed a strong correlation between luminal stenosis of 50% or greater and symptoms of ischemia.[2] However, animal studies of coronary flow reserve (CFR) suggested that 75% stenosis of a coronary artery results in nonlaminar flow and ischemia.[3–6] The differing evidence has resulted in a variety of definitions of disease. The CASS study originally defined disease as equal or greater than 70% stenosis of the LAD, LCX, and the RCA while left main disease was defined as equal or greater than

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50% stenosis.[4] However, the Cooperative Trialists study, based on a combining of the data from all of the randomized trial of CABG, defined disease as equal or greater than 50% stenosis of any major coronary artery.[5] While studies have shown that coronary events can occur when lesions less than 50% stenosed rupture,[6-8] these lesions are usually accompanied by high-grade lesions in other vessels.[7] Another problem in estimating the percent stenosis is the presence of diffuse disease. Necropsy studies shown that the percent stenosis of a lesion is underestimated because the surrounding vessel is also diseased.[8-10]

The constantly changing definition of disease has created a problem for evaluating diagnostic tests for ischemia. Various degrees of luminal stenosis have been used as the criterion for defining disease. In a meta-analysis of 152 studies evaluating the diagnostic characteristics of the exercise ECG by Detrano et al.,[8] 77 studies used 50% luminal stenosis as the criteria for defining CAD, 39 studies used 70% luminal stenosis, 35 studies used 75%, and one study used 90%. The lack of a standard definition raises the question of which criteria are best for identifying those with lesions that could be causing angina. In this article, we have reversed the comparison using the ST segment and treadmill scores as the gold standard for ischemia, comparing them to varying degrees of luminal stenosis. The goal of this article is to demonstrate which degree of stenosis best separates patients into those with and those without ischemia for the purpose of evaluating diagnostic tests.

METHODS

Patients were selected from a database of the last 8000 consecutive male patients who underwent clinical evaluation, exercise testing, and coronary angiography at the Long Beach and Palo Alto Veteran Affairs Medical centers. Patients with prior cardiac surgery or interventions, valvular heart disease, left bundle branch block, more than 1 mm ST depression or Wolff-Parkinson-White (WPW) syndrome on their resting electrocardiogram were excluded from the study. Previous cardiac surgery was the predominant reason for exclusion of patients. Since neither medications nor resting ST depression less than 1 mm have been shown to alter the diagnostic accuracy of the test,[9] exclusions were not made for these reasons. We then selected all patients referred to evaluate chest pain possibly due to coronary disease with complete data who had coronary angiography within 4 months of the treadmill test. As is the case for clinical observational studies of this nature, there was no attempt to reduce work up bias. The population available for the study was 1276 patients. A thorough clinical history, medication, and risk factors were recorded prospectively at the time of exercise testing using computerized forms.[10,11]

Exercise Testing

Patients underwent symptom-limited treadmill testing using the United States Air Force School of Aerospace Medicine (USAFSAM)[10] or an individualized ramp treadmill protocol.[11] Before ramp testing, the patients were given a questionnaire to estimate the patient's exercise capacity before the test and thus allowed most patients to reach maximal exercise at approximately 10 minutes.[12] Visual ST-segment depression was measured at the J junction and corrected for pre-exercise ST-segment depression while standing; ST slope was measured over the following 60 ms and classified as upsloping, horizontal, or downsloping if there was 0.5 mm or more depression. The ST response considered was the most horizontal or downsloping ST-segment depression in any of the 12 leads except aVR during exercise or recovery. An abnormal response was defined as 1 mm or more of horizontal or downsloping ST-segment depression. ST depression was measured both by a clinician and computer analysis.

No test was classified as indeterminate,[13] medications were not withheld, and a maximal heart rate target was not used as an endpoint.[14] The exercise tests were performed, analyzed, and reported per standard protocol and utilized a computerized database (EXTRA, Mosby Publishers, Chicago).[15] Decisions for cardiac catheterization were consistent with clinical practice.

The Duke Treadmill Score

Using Cox proportional hazard analysis, Mark and colleagues developed the Duke Treadmill Score originally as a prognostic score.[16,17] However, recent studies have validated the DTS as a diagnostic score.[16] The DTS uses three variables to generate the score: exercise capacity, amount of ST depression, and the degree of angina that occurred during the exercise treadmill test. The Duke Treadmill Score is calculated as:

Exercise time - (5 × ST depression)

- (4 × treadmill angina index)

Exercise time is measured in minutes; ST depression is measured in millimeters; and the treadmill angina is coded from 0 to 2, where 0 is no angina during the treadmill test, 1 is for angina during the test, and 2 is for termination of the test due to angina.

Consensus Diagnostic Score

The clinical and exercise test data were put into the following equation to generate three probability estimates:

$$\text{Probability} = 1 / (1 + e^{-(a + bx + cy \ldots)})$$

where a = intercept, b and c are beta coefficients, and x and y are variable values.

The appropriate coefficients and variables were from the three equations included in the ACC/AHA exercise testing guidelines.[17] Variables included age, symptoms, risk factors, and exercise test responses.

We previously validated a means to make predictive equations more portable and self-calibrating by requiring a consensus for patient classification as to risk of coronary disease.[18-20] We averaged the three computer generated probability scores to produce one averaged score with a resultant probability of disease from 0 to 100%.

Simple Diagnostic Score

The Simple Score was generated at the Palo Alto Veteran Affairs Hospital for use in a male population and validated at the West Virginia University.[18] The Simple Score uses variables chosen in logistic regression and converts them into a linear score. The score gives a larger coefficient to variables that have a higher predictive value for disease and therefore increases the importance of the variable in the score. The resulting Simple Score is calculated as shown in Figure 1.

Angiography

The angiographic results of the patients were recorded and added to a database. The percent luminal stenosis of the left main, left circumflex, left anterior descending, and right coronary arteries were recorded. The percent diameter stenosis was recorded as 40, 50, 60, 70, 75, 80, 90, or 100% stenosis with lesser degrees not coded. The measurements are a mixture of simple visual estimates, calipers at the Long Beach VA, and digital angiography at the Palo Alto VA as is usually the case in clinical practice. The method used was not specified in the clinical catheterization report.

Variables	Code	Add Points
Maximal Heart Rate	Less than 100 bpm=5; 100-130=4; 130-160=3; 160-190=2; 190-220=1; more than 220=0	X 6 =
Exercise induced ST depression	0-1mm=0; 1-2mm=3; more than 2mm=5	X 5 =
Age	0-40=0; 40-55=3; more than 55=5	X 4 =
Angina Pectoris	Definite AP=5; probable=3; non-cardiac=1; none=0	
Hypercholesterolemia	Yes=5; No=0	
Diabetes	Yes=5; No=0	
Treadmill Angina Score	None=0; Angina occurred=3; reason for stopping=5	
Total Points		

Figure 1. Coding of the variables for the Simple Score for men.

Statistical Analysis

The treadmill scores and ST analysis were generated for all 1276 patients. Angiographic results were calculated for cut-points between 40% luminal stenosis to 100% luminal occlusion in the above-mentioned increments. This means that a patient with 50% luminal stenosis in a major coronary artery would have disease at the equal or greater than 50% cut-point but would not have disease at the equal or greater than 60% cut-point. The area under the receiver operating characteristic (ROC) curves were calculated for the ST measurements and the treadmill scores using the angiographic data based on the cut-points. The greater the value for the area under the curve (AUC), the better the score is able to discriminate disease-producing ischemia.

The prevalence of coronary disease will differ according to the angiographic definition. Because ROC curve area can be influenced by the varying prevalence,[19] we performed an additional analysis that normalized the angiographic groups to a prevalence of 50%. This was accomplished by randomly subtracting nondiseased or diseased patients

from the group until a prevalence of 50% was obtained. For example, if a particular angiographic cut-point produced a prevalence of 40%, nondiseased patients would be randomly removed until the prevalence was 50%. Conversely, if the prevalence were 60%, diseased patients would be randomly removed to achieve a prevalence of 50%. This would produce groups of varying size, but as long as the sample size was over 400, no effect of differing sample size on ROC curve areas was expected.

Statistical analysis of the ROC curve data was accomplished by using confidence intervals to determine the statistical significance. The formula used for calculating the confidence interval is CI = SE × Z score. Using a Z score to give us a P value < 0.05 and the standard errors, we were able to determine the confidence intervals for all the area under the ROC curves and determine whether the differences between the AUCs are statistically significant.

Predictive accuracy (PA) was calculated by taking cut-points calculated to match the specificity of 1 mm of ST depression. The cut-points utilized were 70 for consensus, 50 for the simple score, 1 for the DTS, and 1 mm for ST depression. PA is calculated by adding the number of true positives and true negatives and then dividing by the total number of patients. We then used cross tabulation with the clinical cut-points and the different angiographic cut-point data to calculate the PA of the two measurements of ST analysis and the treadmill scores. PA was calculated on the angiographic cut-point data where the disease prevalence was adjusted to 50% to allow comparison between the groups because of different disease prevalence in the complete population based on the changing criteria of disease.

Table 1. Clinical Characteristics of the Target Population

Variables	Total Population
Age (yrs)	59 ± 10
BMI (kg/m^2)	28 ± 4.6
Hypertension	52%
Diabetes	15%
Family history of CAD	43%
Hypercholesterolemia	42%
COPD	6.5%
Smokers	33%
CHF	3.1%
Symptom status	
Typical angina	34%
Atypical angina	52%
Nonanginal chest pain	8%

Table 2. Exercise Test Responses

Variables	
Maximal heart rate (beats/min)	129 ± 24
Maximal SBP (mmHg)	169 ± 29
METs	7.5 ± 3.1
% abnormal ST	38%

RESULTS

Tables 1 and 2 describe the patient characteristics and exercise test responses. The data for the area under the ROC curves without prevalence adjustment is found in Table 3 and in Figure 2. ST segment depression measured by physicians reached its highest ability to discriminate at 75% and 80% luminal stenosis with an area under the ROC curve of 0.71. ST segment depression measured by computer also achieved an area under the ROC curve of 0.727 at the 75% and 80% luminal cut-points. The ROC curves revealed that the simple score achieved the greatest discrimination, with an area under the ROC curve of 0.796 at the 70% and 75% luminal stenosis cut-points. The Consensus score reach its highest ability to discriminate at the 60% luminal stenosis cut-point with an area under the ROC curve of 0.795. Finally, the DTS reached its highest ability to discriminate at the 80% luminal stenosis cut-point with an area under the ROC curve of 0.765. All treadmill scores and ST segment analysis showed that the area under the curve increases to the above luminal stenosis cut-points and then decreases. When disease prevalence was adjusted to 50% for all cut-points, no statistically significant change was found in the area under the ROC curves except when approaching the 100% occlusion cut-point. (P < 0.05) The data for the area under the ROC curves for disease prevalence adjusted to 50% is found in Table 4.

The simple score had the highest predictive accuracy (PA) of 72.3% at the 75% cut-point. Consensus peaked at a PA of 71.8% at the 60% cut-point. The DTS peaked at a PA of 70.6% at the 80% cut-point. Clinician calculated ST analysis peaked at a PA of 67.7% at the 75% cut-point, and computer calculated ST analysis peaked at a PA of

Table 3. Area Under the ROC Curves for ST Measurements and Treadmill Scores at Different Luminal Stenosis Cutpoints

Cut-Point (%)	Clinical ST Measurement	Computer ST Measurement	Consensus	Simple Score	DTS	Disease Prevalence (%)
40	.66	.69	.78	.78	.71	64
50	.67	.71	.78	.78	.727	59
60	.68	.72	.8	.79	.737	54
70	.7	.72	.79	.8	.752	49
75	.71	.73	.79	.8	.762	43
80	.71	.73	.79	.79	.765	41
90	.69	.71	.77	.77	.752	32
100	.68	.71	.74	.75	.713	16

DTS = Duke Treadmill Score.

68.5% at the 75% cut-point. The PA data is shown in Table 5 and Figure 3.

In comparing the area under the ROC curves, only the differences between the 50% luminal stenosis cut-point and the 75% cut-point for the DTS and ST segment depression were statistically significant ($P < 0.05$). The differences between 50 and 75% luminal stenosis cut-points were not statistically significant for the simple score and the consensus of scores. Though not statistically different, the area under the ROC curves for the simple score and the consensus of scores increase and then decrease as the cut-point for percentage luminal stenosis increases.

The described analysis was also repeated for single-vessel disease. However, the number of patients for this group was very small and was therefore not included because of the lack of statistical significance. However, the initial data on 150 patients with a single 40% occluded vessel and this number decreases to less than 50 patients for a > 80% stenosed vessel. We found that most patients with vessels of greater than 80% stenosis also had other lesions of greater than 40% stenosis. Therefore, doing this analysis on single-vessel disease poses a challenge. However, the results we have on single-vessel disease match the data we present in this article. The treadmill scores reveal a trend that 80% stenosis provides the best discriminator of ischemia in single-vessel disease.

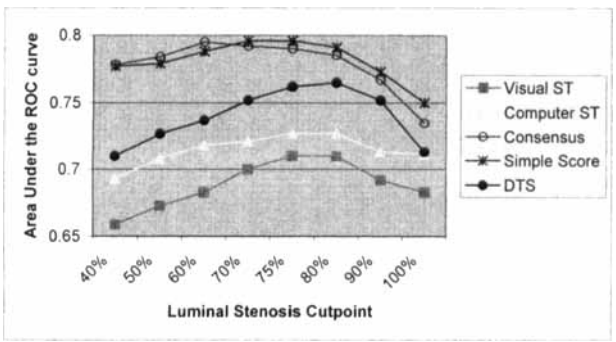

Figure 2. Area under the ROC curves for ST depression and treadmill scores at different luminal stenosis cutpoints.

DISCUSSION

Investigators have used various angiographic criteria for hemodynamically significant coronary lesions to validate diagnostic tests for CAD. Detrano and colleagues showed that 77 studies used 50% diameter narrowing, 70% diameter narrowing in 39 studies, and 75% diameter narrowing in 35 studies. Since the studies each considered their angiographic cut-point to be hemodynamically significant, a clear controversy exists as to whether a 50 or > 70% lesion is a better indicator of ischemia. The meta-analysis concluded that there were no appreciable differences in test characteristics between 50 and 70% diameter obstruction as a criterion for defining disease.

The data from our study reveals that ST analysis discriminates ischemia-causing disease defined as 75% luminal stenosis better than disease that is defined as 50% luminal stenosis. Though this is statistically significant ($P < 0.05$), the actual difference in the predictive accuracy is only about 3% (three more patients out of 100 would be correctly classified). The use of 1 mm of horizontal or downsloping ST depression as a marker of ischemia continues to remain as the commonly accepted approach for discriminating patients with

Table 4. Area Under the ROC Curves for ST Measurements and Treadmill Scores at Different Luminal Stenosis Cutpoints Where Disease Prevalence Is Adjusted to 50%

50% Prevalence Cut-point (%)	Clinical ST Measurement	Computer ST Measurement	Consensus	Simple Score	DTS	Sample Size
40	.665	.706	.787	.782	.719	929
50	.672	.708	.792	.784	.732	1047
60	.683	.720	.798	.792	.741	1183
70	.695	.722	.792	.795	.751	1262
75	.707	.737	.792	.794	.763	1110
80	.704	.729	.785	.788	.765	1048
90	.679	.669	.758	.762	.748	808
100	.665	.583	.726	.743	.71	418

ischemia. However, our study concludes that though 1 mm ST depression is best at discriminating patients with 75% stenosis in any coronary artery, this gold standard shows little difference in its ability to discriminate disease in patients with 50% luminal stenosis in a major coronary artery.

The ability of treadmill scores to predict which patients had disease at different luminal stenosis criteria was very impressive. Though slightly better discrimination occurs at a 75% luminal stenosis cut-point, both the simple score and the consensus of scores had no statistical difference in predicting disease using either a 50 or 75% luminal stenosis cut-point. The DTS was slightly better at predicting ischemic causing disease at 75% luminal stenosis than at 50%. ($P < 0.05$) The main finding of this study was that the treadmill scores were able to predict both disease at 50% luminal stenosis and 75% luminal stenosis with similar accuracy. This reveals that the ongoing debate over luminal stenosis criteria to define disease is resolved and that a criterion of 50% luminal stenosis to define significant angiographic CAD should be sufficient.

An interesting finding of the study is also the increasing ability to discriminate disease until a 75% luminal stenosis cut-point. After this cut-point is reached, the ability to discriminate disease begins to steadily decline. The reason for this decrease in ability to discriminate disease is most likely due to the changing cut-point. A patient may have disease that produces ischemia and a positive treadmill score but might not have a lesion that would place them as having disease defined by the 90 or 100% luminal occlusion cut-point. This means that these patients with hemodynamically significant lesions would be considered false positives because they might have ST depression greater than 1 mm or a positive treadmill score but there 75% luminal stenosis is not considered disease by the 90 or 100% luminal occlusion cut-point. Another possible factor in the decreasing predictive accuracy of ST depression and the treadmill scores is the presence of collaterals in occluded vessels. A patient with a 90% occluded vessel may not experience ischemia and have a negative test if collaterals are present.

Recent studies have revealed a great deal about the pathophysiology resulting in ischemia. Topol and Nissen[20] stress the need to reevaluate angiography as the "gold standard" for determining

Table 5. Predictive Accuracy for ST Measurements and Treadmill Scores at Different Luminal Stenosis Cutpoints Where Disease Prevalence Is Adjusted to 50%

50% Prevalence Cutpoint (%)	Clinical ST Measurement (%)	Computer ST Measurement (%)	Consensus (%)	Simple Score (%)	DTS (%)	Sample Size
40	64.6	66.4	70.5	70.4	66.1	929
50	65.1	65.9	71.3	70.4	67.5	1047
60	65.8	66.5	71.8	71.3	68.3	1183
70	66.6	67.0	71.0	71.9	69.2	1262
75	67.7	68.5	71.0	72.3	70.5	1110
80	67.2	68.0	70.7	71.7	70.6	1048
90	64.4	61.4	68.5	70.1	68.3	808
100	62.4	53.8	68.1	66.6	64.0	418

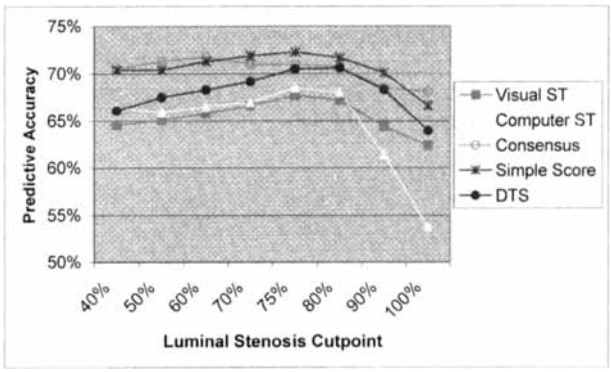

Figure 3. Predictive accuracy of ST Depression and treadmill scores at different luminal stenosis cut-points.

whether a lesion is hemodynamically significant. The use of flow wires and intracoronary ultrasound may greatly aid angiographers in determining which lesions are ischemic.[21] In a recent study by Briguori and colleagues,[22] all patients with a coronary luminal area stenosis less than 70% had a fractional flow reserve greater than 0.75 and are therefore not likely to have ischemia in those arteries. Wilson and colleagues[23] found that an increase in flow of 2.5 above the baseline or less after vasodilation predicted ischemia with a sensitivity of 100% when comparing coronary flow reserve with exercise-induced ST depression. This same study found that an increase in flow of 3.5 above baseline had a sensitivity of 82% and a specificity of 87%. These studies reveal that the use of flow wires and intracoronary ultrasound may provide a better means of diagnosing hemodynamically significant lesions than by angiography alone.

This study is meant to provide physicians with data on the diagnostic accuracy of treadmill scores and show the best angiographic criteria for discrimination of ischemia. However, this study is not suggesting what angiographic criteria should be used to define disease amongst patients. The Cooperative Surgery Trialists suggest a 50% luminal stenosis cut-point as a criterion for defining disease. The suggested cut-point is to aid in determining whether a patient should undergo revascularization surgery and is not necessarily the best criteria for evaluating diagnostic tests. This brings up the question as to which angiographic criteria should be used when creating a treadmill score to achieve the highest predictive accuracy based on angiographic results.

The prediction of patients with lesions less than 50% stenosis is difficult because they do not usually have ischemia. There is no data that show patients with MI resulting from rupture of lesions < 50% could be prevented. Studies that evaluated patients previous to MI in a lesion < 50% were often evaluating the patient because lesions greater than 50% were also present and produced ischemia. However, it seems that most patients that are at risk for an MI resulting from rupture of a vessel less than 50% stenosed will not experience angina and therefore do not present until after the MI occurs. The ability to predict which lesions will rupture can be valuable for patients undergoing angiography, but the ability to determine patients at risk in a nonischemic population will prove most difficult with any type of stress testing.

In conclusion, our data reveal a trend that 75% luminal stenosis serves as a better criterion for discriminating ischemia, but as a criterion for diagnostic test evaluation, any lesion cut point between 50 and 80% is reasonable.

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