EVALUATION OF THE EXERCISE ELECTROCARDIOGRAM BY THE ST SEGMENT/HEART RATE SLOPE

PAUL KLIGFIELD, M.D., OLIVIER AMEISEN, M.D.,
PETER M. OKIN, M.D. AND JEFFREY S. BORER, M.D.

Division of Cardiology
Department of Medicine
The New York Hospital-Cornell Medical Center
New York, New York

ALTHOUGH for many years exercise electrocardiograms have been widely used for the evaluation of patients with suspected ischemic heart disease, standard electrocardiographic criteria have poor sensitivity for the detection of coronary artery disease and poor positive predictive value for coronary disease in populations with a low prevalence of coronary obstruction.[1-3] In addition, the clinical value of exercise electrocardiograms in patients with typical angina pectoris is limited by poor test accuracy for the identification of anatomically and functionally severe coronary disease.[4,5] These problems, together with the significantly improved test sensitivity and specificity of methods based on radionuclide imaging,[6] have reduced clinical confidence in the value of routine exercise electrocardiography for the assessment of the presence and severity of myocardial ischemia. Because the exercise electrocardiogram is available and easily accessible to most patients, improved test accuracy remains an important goal. It is therefore useful to review the clinical value and limitations of a recently developed physiologic approach to analysis of the exercise electrocardiogram that provides important insight into the nature and extent of underlying coronary disease.

THE ST/HR SLOPE

The ST/HR slope, which examines rate-related changes in ST segment depression during exercise, has been demonstrated by Linden and coworkers to distinguish accurately patients with and without coronary artery disease and to separate patients with coronary obstruction according to the pre-

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cise number of coronary arteries involved.[7-9] Improved accuracy of exercise electrocardiograms using the ST/HR slope method has been confirmed in several other laboratories.[10-15] Since it had previously been observed that ST segment depression in patients with coronary obstruction is often linearly related to changes in heart rate during exercise,[16] this method is based on sound physiologic reasoning. At higher levels of effort, heart rate is directly related to myocardial oxygen demand,[17] while ST segment depression reflects the extent of myocardial ischemia.[18] Thus, by normalizing the ST segment depression that occurs during exercise for corresponding exercise-induced changes in heart rate, the ST/HR slope should more accurately reflect the anatomic and functional extent of underlying coronary obstruction than does the magnitude of ST segment depression alone.[19]

Calculation of the maximum ST/HR slope is performed using linear regression analysis to relate changes in ST depression to changes in heart rate according to the method of least squares. Because the slope of the ST/HR relationship tends to become steeper at higher workloads and the maximum ST/HR slope is sought as the test result, regression analysis begins at the peak of exercise and incorporates progressively earlier data. In each electrocardiographic lead analyzed, the final three data points relating heart rate and corresponding ST depression are tested for linearity. Regression analysis continues in each lead by progressive inclusion of earlier data points, and the highest ST/HR slope associated with a statistically significant coefficient of linearity is taken as the test result for that lead (Figure 1). The highest significant slope from among all leads tested is then taken as the maximum ST/HR slope for the patient.

In the studies reported from Leeds,[7-9] all 12 standard electrocardiographic leads and, in addition, lead CM5 were used to derive the maximum ST/HR slope. Our initial experience with the ST/HR slope[10-12] has been based on a modified analysis that uses only leads V5, V6, and aVF. Therefore, the data in the present report are biased against the method, since evaluation of only three leads may result in marked underestimation of the maximum ST/HR slope. Our prospective ST/HR slope trial currently incorporates 13 leads. Calculation of the ST/HR slope is obviously time consuming when performed from manual measurements of ST segments. However, improved computer-based methods of ST segment measurement have greatly simplified the ST/HR slope calculation,[20] and on-line linear regression analysis should soon be available for immediate calculation of the maximal ST/HR slope at the completion of exercise.

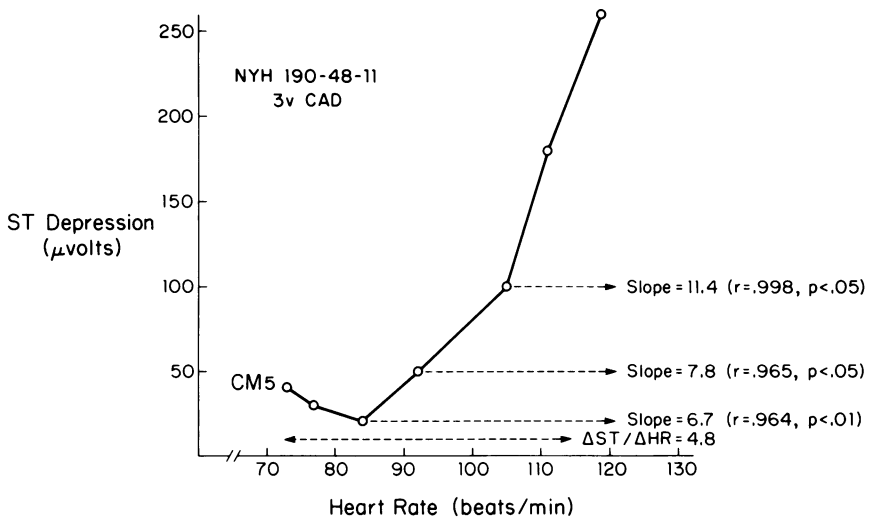

Fig. 1. Calculation of the ST/HR slope. ST segment depression in lead CM5, measured in μV (vertical axis), is plotted against exercise-induced change in heart rate (horizontal axis) for a patient with three-vessel coronary artery disease. The slope of the line relating the final three data points is compared with the slope of lines incorporating progressively earlier data points, and the highest slope that is statistically significant by standard linear regression methods is taken as the test finding for the lead. Because ST segment depression changes more rapidly at higher heart rates, this value is not the same as the value obtained by simply dividing the amount of ST depression at end-exercise by the change in heart rate. Reproduced by permission from Kligfield, P., Okin, P.M., Ameisen, O., Borer, J.S.: Evaluation of coronary artery disease by an improved method of exercise electrocardiography: the ST segment/heart rate slope. *Am. Heart J. 112*:589-98, 1986.

Clinical Value and Theoretical Limitations of the ST/HR Slope

We have found that analysis of the ST/HR slope can significantly improve the sensitivity, specificity, and predictive value of exercise electrocardiograms for the recognition of patients with three-vessel and functionally severe two-vessel coronary artery disease in patients with stable angina pectoris,[10-12] and similarly positive findings have been reported from other laboratories.[13-15] In addition, the ST/HR slope also seems to improve the sensitivity of exercise electrocardiograms for the detection of coronary disease, while preserving a high level of test specificity.[11]

However, considerable criticism of the method has followed several unsuccessful attempts to reproduce the near-perfect accuracy of the original ST/HR slope reports for the identification of the extent of coronary artery disease.[21,22] It is our position that this criticism, based on the question of test perfection, is misdirected; surely no biologic test can be expected to per-

form perfectly, and thus demonstration of test imperfection does not address the more important issue whether the test represents a significant improvement over currently available methodology for the achievement of clinically useful results. A more scientifically valid criticism emerges from challenges to the theoretical basis of the method.[23] Clearly, variable extent of luminal coronary artery obstruction, variable transmural perfusion, variable effects of serial lesions, and variable coronary collateral supply should make precise correlation of the ST/HR slope with the exact number of obstructed vessels unlikely. Further, it is well recognized that patients often have negative exercise test responses despite obvious coronary artery disease following recent myocardial infarction,[24,25] while, conversely, patients with aortic regurgitation often have positive standard exercise test responses despite demonstrably normal coronary arteries.[26] These repolarization findings might be expected to affect the ST/HR slope and make prediction of the number of obstructed coronary vessels by this method unlikely.

Therefore, we examined the relation of the ST/HR slope to the underlying anatomic and functional extent of coronary artery disease in patients with stable angina pectoris and separately in patients with recent myocardial infarction and with aortic regurgitation.[10-12,27] Our findings highlight the value of the ST/HR slope method for identification of extensive coronary disease in patients with stable angina, and also indicate the limitations of the method in other clinical populations. While the test is not a perfect predictor of the number of obstructed coronary arteries, it appears to represent a significant advance in exercise electrocardiography.

Sensitivity of the ST/HR Slope for the Detection of Coronary Disease

In a group of 50 patients with stable angina pectoris who underwent cardiac catheterization there were 46 patients with greater than 75% luminal obstruction of one or more major coronary artery systems (left anterior descending, left circumflex, or right coronary artery). Five patients had left main coronary artery disease, and in each case this was associated with coincident three-vessel coronary disease. The ST/HR slopes in these 46 patients are shown in Figure 2, along with calculated ST/HR slopes in clinically normal subjects, patients studied following recent myocardial infarction, and patients with aortic regurgitation.

Among the 46 stable angina patients with coronary disease, the mean maximal ST/HR slope was 5.5 ± 0.6 (standard error of the mean) μV/beat/min, ranging from 0.7 to 20.0. In this group of patients, 91% (42/46) had ST/HR

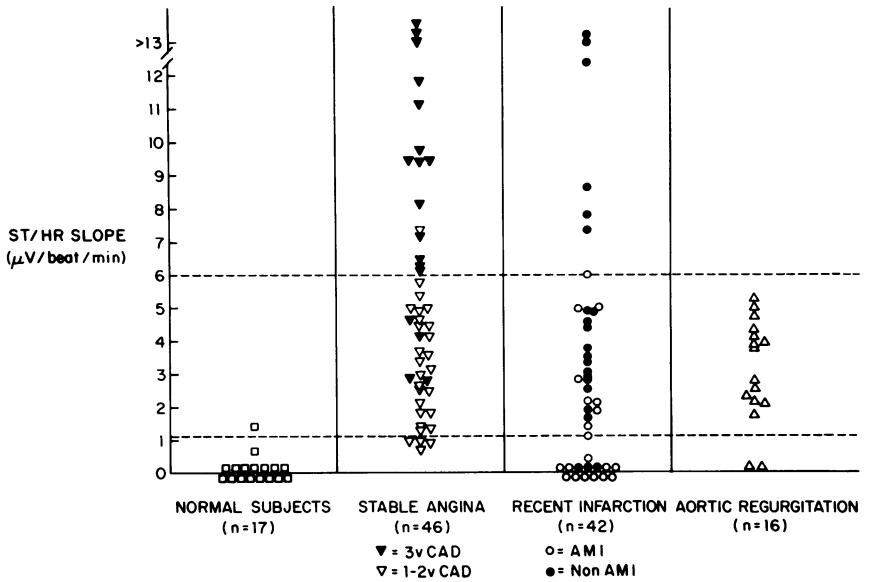

Fig. 2. The ST/HR slope in clinically normal subjects, patients with stable angina pectoris due to coronary disease, patients with recent myocardial infarction, and patients with aortic regurgitation without coronary disease. The line at a slope of 1.1 μV/beat/min represents the upper limit of normal in studies by Linden and colleagues, and the slope of 6.0 represents the partition used for the recognition of three-vessel disease. Reproduced by permission from Ameisen, O., Okin, P.M., Devereux, R.B., et. al.: Predictive value and limitations of the ST/HR slope. *Br. Heart J. 53*:547-51, 1985.

slopes exceeding 1.1, while 9% (4/46) had slopes less than 1.1. Thus, the sensitivity of the ST/HR slope for the detection of coronary disease in this population was 91%, using the test criterion of 1.1 μV/beat/min reported in studies from Leeds. In contrast, the test sensitivity of standard electrocardiographic criteria (defined as horizontal or downsloping ST segment depression equal to or greater than 0.1 mV) was only 57% (26/46) in these patients.

The partition value of 1.1 μV/beat/min used in our patients is based on the upper limit found in subjects without significant coronary disease by Linden and colleagues.[7-9] However, their studies were performed using upright bicycle ergometry and 13 electrocardiographic leads, while our studies[10-12] used upright treadmill exercise with three electrocardiographic leads and manual measurement of ST segment depression at 70 msec after the j-point. In our ongoing prospective ST/HR slope studies, we are using 13 leads (in-

cluding bipolar CM5) with computer-based, signal-averaged ST segment measurement at 60 msec after the j-point. Thus, the partition values reported here for three-lead treadmill exercise tests are likely to change as further experience is accumulated with more detailed methodology.

In the 17 clinically normal subjects, each of whom had normal echocardiograms and normal rest and exercise radionuclide cineangiograms, test specificity was 94%, since 16 of 17 had ST/HR slopes less than 1.1. Test specificity of standard exercise electrocardiographic criteria was 100% in this group. Thus, our findings suggest that analysis of the ST/HR slope can markedly improve exercise electrocardiographic sensitivity for the detection of coronary artery disease without significant reduction in test specificity. However, it should be noted that these data were obtained in patients with symptomatic, stable angina pectoris. Whether similar improvement in test sensitivity will be found in the important population of asymptomatic subjects with coronary disease remains to be tested.

Recognition of Anatomically Extensive Coronary Artery Disease

Among the 50 patients with stable angina were 18 with three-vessel coronary artery disease, including five with additional left main coronary disease, and 22 with two-vessel disease, six with one-vessel disease, and four with no significant coronary disease. Maximum ST/HR slopes are shown in relation to the extent of coronary artery disease in Figure 3.

It is apparent from the figure that the exercise electrocardiographic ST/HR slope tends to increase with increasing numbers of obstructed coronary arteries. The mean ST/HR slope in the patients with three-vessel coronary disease was 9.1 ± 1.2 μV/beat/min, which was significantly higher than the mean ST/HR slopes for patients with two-vessel disease (3.5 ± 0.4), patients with one-vessel disease (2.2 ± 0.5), and patients with no coronary disease (1.3 ± 0.3).

More important, an ST/HR slope partition of 6.0 μV/beat/min identified patients with three-vessel disease in this population with a sensitivity of 78% (14/18), specificity of 97% (31/32), and positive predictive value of 93% (14/15). In contrast, test sensitivity of 78% for recognition of three-vessel disease by standard electrocardiographic criteria was associated with a specificity of only 56% in these patients. Combined criteria which incorporated either early onset of a positive standard response, prolonged positive re-

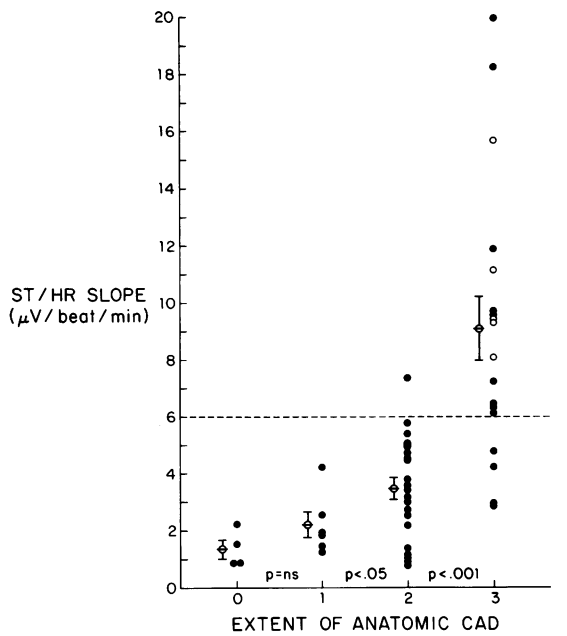

Fig. 3. Relation of the calculated ST/HR slope to the anatomic extent of coronary artery disease (75% luminal obstruction) in 50 patients with stable angina pectoris. The open circles represent patients with additional left main coronary artery disease. A slope value of 6.0 μV/beat/min represents the partition used for the recognition of three-vessel coronary artery disease. Reproduced by permission from Okin, P.M., Kligfield, P., Ameisen, O., et. al.: Improved accuracy of the exercise electrocardiogram: Identification of three vessel coronary disease in stable angina pectoris by analysis of peak rate related changes in ST segments. *Am. J. Cardiol. 55*:271-76, 1985.

sponse, or more extreme ST segment depression improved specificity for three-vessel disease to only 72–75%. Further, these criteria reduced test sensitivity to 44–61%.

These findings suggest that the ST/HR slope has important predictive value for the identification of patients with anatomically extensive coronary artery disease. The method appears to be valid even in the presence of beta-blocking drugs[9,10] since the reduction in ST segment depression with these agents is matched by a proportional reduction in exercise-induced change in heart rate. The effects of digitalis preparations, calcium blocking drugs, and the nitrates on the ST/HR slope require clarification.

Thus, we have not found the ST/HR slope a perfect predictor of the precise anatomic extent of extramural coronary obstruction. Indeed, from the theoretical considerations outlined above, we would not expect such findings. However, when high ST/HR slopes are associated with less than three-

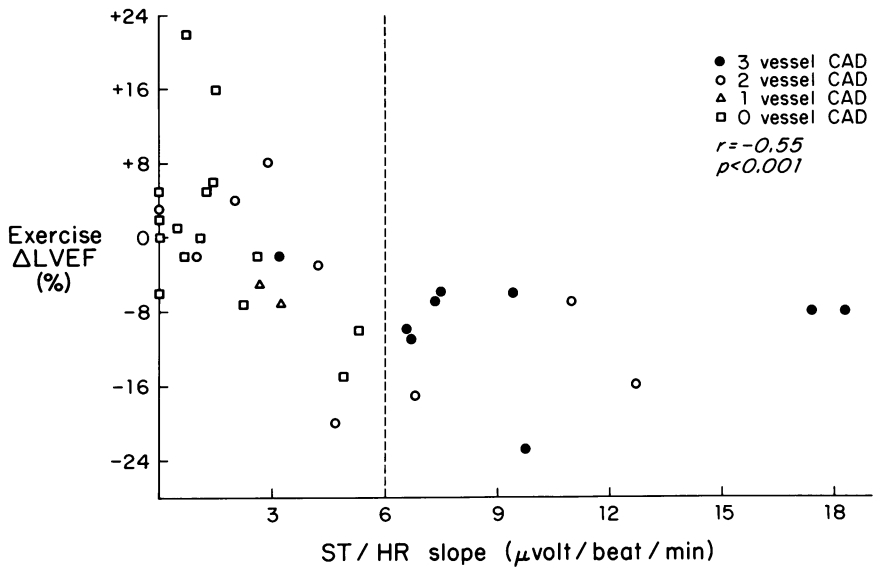

Fig. 4. Relation of the calculated ST/HR slope to the functional extent of coronary disease as estimated by the exercise-induced change in left ventricular ejection fraction in 35 patients with stable angina. Patients with high ST/HR slopes have greater decreases in ventricular performance with exercise, suggesting functionally severe ischemia. Reproduced by permission from Kligfield, P., Okin, P.M., Ameisen, O., et. al.: Correlation of the exercise ST/HR slope in stable angina pectoris with anatomic and radionuclide cineangiographic findings. *Am. J. Cardiol. 56:*418-21, 1985.

vessel disease, physiologically severe coronary obstruction is apparent from the associated marked fall in exercise left ventricular ejection fraction determined by radionuclide cineangiography in this subset of patients.[12] The relationship of the ST/HR slope to the exercise-induced change in left ventricular ejection fraction is shown for 35 patients with stable angina in Figure 4. In these patients an inverse correlation was found between these variables ($r = -0.55$, $p < 0.001$), so that increasing ST/HR slopes were associated with increasingly large falls in left ventricular performance. Despite the absence of three-vessel coronary disease in some patients with high ST/HR slopes, functionally severe disease can be demonstrated by the magnitude of ejection fraction change with exercise.

The ST/HR Slope Following Recent Myocardial Infarction

We also examined 49 patients who had exercise testing performed during the predischarge phase of recent myocardial infarction and who also underwent coronary angiography.[11,27] In this group a statistically valid ST/HR

slope could not be calculated in six patients and, of the patients with calculable slope values, three had no significant coronary artery disease. There were eight patients with three-vessel disease.

In this recent myocardial infarction population, the ST/HR slope was not accurate for the identification of patients with coronary disease or for the identification of patients with anatomically extensive coronary obstruction. Only 54% (25/46) of the patients with coronary disease had ST/HR slope values greater than 1.1 μV/beat/min. This is significantly lower than the test sensitivity of this partition in patients with stable angina. After recent infarction, test sensitivity was most reduced in patients with Q-wave infarction (42%, 13/31), particularly those with anterior wall infarction (32%, 7/22), but remained moderately high in patients with non-Q-wave infarction (80%, 12 of 15, $p<0.05$ compared with Q-wave infarction).

The mean ST/HR slope in six patients with three-vessel disease who had calculable test values was 7.9 μV/beat/min, with a range from 0.0 to 18.7; two additional patients with three-vessel disease had noncalculable slopes. Sensitivity of an ST/HR slope partition of 6 μV/beat/min for the detection of three-vessel disease in this group was only 37% (3/8). This was confirmed by evaluating ST/HR slope findings in an additional group of six postinfarction patients with three-vessel disease, five of whom had test values less than 6. Thus, the sensitivity of the ST/HR slope for three-vessel disease in the combined groups was only 29% (4/14).

These findings suggest that the sensitivity of the ST/HR slope is markedly reduced in patients after recent anterior Q-wave injury, but not necessarily after other types of infarction, and this represents an important limitation of the method. This limitation is shared by the standard exercise electrocardiogram, in which false negative test responses following recent infarction are well recognized.[16,17] The mechanism underlying these false negative test results requires further investigation, but they seem to be at least partly related to inadequately opposed persistent ST segment elevation during the healing phase of Q-wave infarction. Further limiting the applicability of the ST/HR slope following recent infarction is the relatively high prevalence of noncalculable slopes. Since this was predominantly due to inadequate data points in patients with poor effort tolerance, it is likely that this problem will be solved by revision of the standard exercise protocol to include smaller workload increments during early effort.[20]

The ST/HR Slope in Aortic Regurgitation

Among the 17 patients with aortic regurgitation who had normal coronary arteries at catheterization, a statistically valid ST/HR slope could not be cal-

culated in one patient. In the 16 remaining patients, the mean ST/HR slope was 3.1 ± 0.4 μV/beat/min, ranging from 0.0 to 5.3. ST/HR slope values that exceeded 1.1 μV/beat/min were found in 88% (14/16) of these patients despite the absence of coronary disease, in contrast to only 6% (1/17) of the clinically normal population ($p < 0.001$). Of note, no patient with aortic regurgitation had an ST/HR slope that exceeded 6 μV/beat/min, the partition previously found to be highly accurate for the detection of three-vessel coronary disease in patients with stable angina pectoris.

These data suggest that nonischemic diseases affecting the left ventricle can also affect the ST/HR slope, and this represents another potential limitation of the method. This is consistent with previous observations that standard exercise test criteria are often positive in patients with valvular heart disease,[26] even in the absence of coronary obstruction. Of course, this limitation does not invalidate the ST/HR slope approach, since it can be argued that even in the absence of coronary disease, the high wall stress and reduced coronary flow reserve in patients with important aortic regurgitation might result in subendocardial ischemia during exercise.[28] However, these findings indicate the importance of patient selection in testing the applicability and accuracy of any new method.

Clinical Implications

The ST/HR slope, a new method of analysis of the exercise electrocardiogram, appears to be a highly sensitive and specific technique for improved detection of the presence and severity of coronary artery disease in patients with stable angina pectoris. Test sensitivity of the ST/HR slope for the identification of coronary disease exceeds that of standard exercise electrocardiographic criteria, with specificity that remains high. Further, within the stable angina population, the ST/HR slope is useful for identification of patients with three-vessel or with functionally severe two-vessel coronary artery disease. These findings should strengthen the role of exercise electrocardiography in the evaluation and management of patients with chest pain syndromes.

However, it is important to recognize limitations of the ST/HR slope method. Recent myocardial infarction, particularly Q-wave infarction of the anterior wall, is associated with significantly reduced test sensitivity for the presence of underlying coronary artery disease. Conversely, aortic regurgitation, and presumably other abnormal cardiac loading conditions, can be associated with significantly reduced test specificity with regard to underlying coronary artery disease. Therefore, despite impressive test accuracy in patients with stable angina, false positive and false negative test responses

with respect to the extent of coronary disease can occur in these situations. These findings indicate that the ST/HR slope is not a perfect predictor of the anatomic extent of coronary obstruction. However, we do not believe that simple recognition of these specific limitations of test applicability should obscure the otherwise striking improvement in exercise electrocardiography afforded by ST/HR slope analysis.

On the other hand, these limitations, in addition to methodologic differences, might partly explain varying reports of ST/HR slope accuracy. For example, the patients studied by Quyyumi et al.[21] were not clearly characterized with respect to recent infarction or the possible presence of additional valvular disease. The patients reported by Balcon et al.[22] did not have any valvular disease, but a substantial proportion had prior myocardial infarction, including their only two patients who had three-vessel coronary disease. Thus, admixture of patients with varying proportions of recent infarction and nonischemic disorders can substantially alter the relationship between ST/HR slope findings and the underlying extent of coronary obstruction. However, these patients are generally simple to identify during pre-exercise clinical evaluation so that these limitations need not reduce test accuracy in the larger population of patients with stable angina in whom the method may be most usefully applicable.

Further study will focus on simplification of ST/HR slope analysis by means of computer technology further to increase test applicability. Use of modified treadmill exercise protocols to produce smaller heart rate increments between stages should improve test accuracy, since the ST/HR slope calculation strongly depends on detection of the maximum rate of ST segment shift, which can occur during small heart rate changes. Establishment of test specificity in a broader range of clinically normal subjects is needed, and partition criteria may change as further experience is gained with more detailed methods of ST/HR slope analysis.

SUMMARY

The ST segment/heart rate (ST/HR) slope is a recently developed method of analysis of the exercise electrocardiogram that can improve test sensitivity for the detection of coronary artery disease and can identify patients with anatomically and functionally severe coronary obstruction with significantly greater accuracy than is currently available using standard test criteria. The ST/HR slope, in effect, normalizes the amount of exercise-induced ST segment depression for the corresponding change in heart rate. Since heart rate is strongly related to myocardial oxygen demand during exercise, the ST/HR

slope provides an estimate of the extent of disease based on correction of the electrocardiographic estimate of myocardial ischemia for associated increments in myocardial work. Sensitivity of the ST/HR slope for the detection of coronary disease in a population of patients with stable angina was 91%, compared with only 57% using standard test criteria. Further, an ST/HR slope partition for the recognition of three-vessel coronary disease had a sensitivity of 78%, specificity of 97%, and positive predictive value of 93% in patients with stable angina. However, test sensitivity was significantly reduced following recent myocardial infarction, while test specificity was significantly reduced in patients with aortic regurgitation but who had normal coronary arteries. Thus, while limitations of the method must be recognized, the ST/HR slope has important diagnostic power in patients with stable angina.

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