JACC Vol. 19, No. 1
January 1992:11–8

Exercise-Induced ST Depression and ST/Heart Rate Index to Predict Triple-Vessel or Left Main Coronary Disease: A Multicenter Analysis

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The aim of this investigation was to determine the difference in accuracy between two frequently published noninvasive indicators of severity of coronary artery disease (exercise-induced ST segment depression and heart rate-adjusted ST depression [ST/HR index]). The study was designed as a survey of consecutive patients undergoing exercise electrocardiography and coronary angiography. There were a total of 2,270 patients without prior myocardial infarction or cardiac valvular disease referred for angiography from eight institutions in three countries; 401 of these patients had triple-vessel or left main coronary artery disease.

The sensitivities of ST depression and ST/HR index in detecting triple-vessel or left main coronary artery disease were, respectively, 75% and 78% ($p = 0.08$) at cut point values where their specificities were equal (64%). This small increase in the accuracy of the ST/HR index was evident only at peak exercise heart rates below the median value of 132 beats/min, where the sensitivities of ST depression and ST/HR index were 73% and 76% ($p = 0.03$), respectively, at cut point values corresponding to a specificity of 60%. These results were consistent at all eight participating institutions.

The increase in accuracy achieved by dividing exercise-induced ST depression by heart rate is small and confined exclusively to a low exercise heart rate. This lack of superiority cannot be generalized to all methods of heart rate adjustment.

(J Am Coll Cardiol 1992;19:11–8)

The high mortality rate among patients with triple-vessel or left main coronary artery disease has encouraged exercise electrocardiographers to search for criteria that might distinguish these patients from others. Because such patients may have a reduced mortality rate when treated surgically (1–3), the preangiographic identification of these patients would increase the cost-effectiveness of their evaluation.

One approach toward a more accurate discrimination between patients with and without triple-vessel or left main coronary artery disease has been to adjust the exercise-induced ST segment depression by the accompanying heart rate (HR) increase. Several methods have been proposed: the ratio of the ST area and the heart rate (4), the maximal ST/HR slope in all electrocardiographic (ECG) leads (5); the maximal ST/HR slope in three ECG leads (6); the ratio between the sum of ST depressions in 12 ECG leads and the heart rate (7); the ratio between ST depression and heart rate (8) (called *ST/HR index* by Kligfield et al. [9]) and a multivariate model that takes into account the ST/HR slope, the achieved heart rate and the slope of ST depression (10).

The purpose of the present investigation was to 1) test the effectiveness of the ST/HR index for predicting triple-vessel or left main coronary artery disease in patients from eight centers who had no prior myocardial infarction and were referred for angiographic evaluation, and 2) to determine which clinical and stress variables account for any observed differences in accuracy between the ST/HR index and the conventional ST depression criterion.

Methods

Study patients. The study group consisted of consecutive patients referred for coronary angiography at each of the institutions listed in Table 1. Only patients with an interpret-

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Manuscript received March 19, 1991; revised manuscript received June 10, 1991, accepted June 28, 1991.

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0735-1097/92/$3.50

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Table 1. Clinical Characteristics of the Study Group of 2,270 Patients From Eight Institutions

	Chicago	Cleveland	Long Beach	Basel	Budapest	Geneva	Rotterdam	Zurich	Overall
Patients (no.)	122	303	201	79	670	543	295	57	2,270
Clinical data									
Mean age (yr)	59 ± 9	54 ± 9	60 ± 8	55 ± 8	48 ± 8	54 ± 9	51 ± 10	54 ± 10	[illegible] ± 10
Men (%)	75	68	98	85	69	81	75	93	78
Typical angina (%)	62	48	72	72	40	61	51	74	54
Stress test									
ST ↓ ≥1 mm (%)	73	45	66	29	37	37	38	49	43
Peak HR (beats/min)	139 ± 24	150 ± 23	125 ± 22	116 ± 24	137 ± 23	126 ± 22	125 ± 25	136 ± 27	133 ± 25
Ex angina (%)	46	33	61	53	29	38	45	28	38
Beta-blocker use (%)	25	33	33	37	14	37	—	58	28
Protocol	TM	TM	TM	BK	BK	BK	BK	BK	
Ex patients referred for angiography (%)	30	—	29	87	20	40	60	90	—
Coronary angiography									
≥1 vessel disease (%)	77	46	76	63	39	[illegible]	70	74	57
≥2 vessel disease (%)	53	26	48	58	25	32	46	26	35
3-vessel or left main disease (%)	28	16	27	30	12	13	21	12	18

BK = bicycle ergometer; Ex = exercise; HR = heart rate; ST ↓ = ST segment depression; TM = treadmill.

able exercise ECG and coronary angiogram were included. An exercise ECG was considered interpretable when left bundle branch block was not present and when muscle artifact, baseline wander and other "noise" did not make measurement of ST segment depression impossible. More than 90% of tracings were interpretable at all of the institutions. Patients with myocardial infarction and those with suspected or known valvular heart disease or cardiomyopathy were excluded.

Data collection was part of an international multicenter collaboration. For the sake of uniformity, all data were prospectively collected (11). Data collection was thus similar to that used during other evaluations of heart rate adjustment (6,8,9,12). At two institutions (Cleveland and Rotterdam), data were collected prolectively as well as prospectively (13). The definitions of clinical and test results were defined a priori. Each institution was allowed to use its routine exercise protocol. At three institutions, the same patients had been described in previous clinical reports (8,14,15).

Clinical variables. Clinical data collected at all institutions included age, gender and chest pain characteristics. The latter were classified into four categories: 1) *typical angina pectoris*, defined as pain that occurs in the anterior thorax, neck, shoulders, jaw or arms and is precipitated by exertion and relieved within 20 min by rest; 2) *atypical angina*, defined as pain in one of these locations that is either not precipitated by exertion or not relieved by rest within 20 min; 3) *nonanginal pain*, defined as pain that is not located at any of these sites or, if so located, is not related to exertion and lasts <10 s or >30 min; and 4) *asymptomatic*, defined as no pain.

Exercise test variables. All patients underwent symptom-limited upright exercise. A standard 12-lead ECG was recorded periodically during exercise, at maximal effort and during recovery. At all institutions, manual measurements similar to those previously reported (8) of the ECG lead with the maximal ST depression related to rest were used for analysis. In the three U.S. institutions, treadmill protocols (either Bruce or Balke-Ware) were used. In the five European laboratories, a bicycle ergometer was used. The exercise data collected included medications at the time of the exercise test, duration of the exercise test, heart rate at rest, maximal achieved heart rate, rest and peak exercise systolic and diastolic blood pressures, exercise-induced angina, exercise-induced ST depression relative to rest and exercise-induced ST slope. Measurements of ST depression at rest and during exercise were performed at one institution by an investigator who, for research purposes (8), was denied access to all patient data and by the physician supervising the test at the others. Clinical data and exercise test results were recorded before coronary angiography and therefore were obtained without knowledge of the angiographic results.

The ST depression was evaluated as the difference between the rest and peak exercise ST depression measured 0.08 ms after the J point; it is expressed in mV. Because the ST/heart rate (HR) index does not utilize information about the slope of ST depression, we ignored slope in our conventional analysis as well.

The ST/HR index was calculated as the ratio of the difference between exercise and rest ST depression and the difference between exercise and rest heart rate as previously described (8); it is expressed in μV/beats per min.

Referral for coronary angiography. The process of referral for coronary angiography was complex. Factors affecting the decision to perform an angiogram included age, gender, clinical symptoms, risk factor profile, exercise test results, availability of an angiographic suite, method of reimbursement and philosophy and attitudes of patients and physicians. At all eight institutions, clinical symptoms affected the decision to refer patients for exercise testing and coronary angiography. At all institutions except Cleveland, the exercise test result also affected the decision to refer for angiography. In Cleveland, the exercise test was part of a research project and the results were unknown to the physician making the referral decision. Of all eight institutions, only Long Beach and Chicago can be considered primary care facilities for the purpose of this study. At the other institutions, most subjects were referred from outside hospitals for exercise testing and angiography.

Coronary angiography. Coronary angiograms were obtained within 60 days after the noninvasive evaluation. They were interpreted as a routine hospital procedure. Because the exercise tests and angiograms were performed in a clinical setting, the results of the former were known to the physicians interpreting the latter. At two institutions, the exercise test results were not known to the cardiac angiographers and referring physician so that the decision to perform coronary angiography was not influenced by these results. To assess the influence of the clinical data on the interpretation of the angiograms, 30 angiograms from patients with and 30 from patients without triple-vessel or left main coronary artery disease were randomly chosen for evaluation by an angiographer who had no access to clinical information or to the previous interpretation. In only five cases (8%) was there disagreement between the two interpretations. In one case, the disagreement could be ascribed to the influence of the clinical and exercise variables; the other four disagreements could be explained by interobserver variability.

Triple-vessel or left main coronary artery disease was defined by an obstruction of ≥50% of the normal diameter of at least three major coronary arteries or the left main coronary artery. Major coronary vessels were considered the left anterior descending, left circumflex (including obtuse marginal branches) and the right coronary artery (including the posterior descending branch). The maximal percent diameter narrowing in each major vessel was assessed visually by an experienced angiographer at each institution who based the assessment on views of the vessels in more than one plane.

Statistical analysis. To compare ST and ST/HR index criteria, the usual clinical cut point of 0.1-mV ST depression was adopted as the standard criterion. Sensitivity and specificity at this point regarding the diagnosis of triple-vessel or left main coronary artery disease were calculated according to standard definitions (16). The ST/HR index cut point giving the same specificity of 0.1-mV ST depression was determined and the sensitivity calculated and compared with that of the ST depression of 0.1 mV. The analysis was also performed for the two groups of patients whose peak heart rate was lower or exceeded the median peak heart rate (132 beats/min). The McNemar chi-square test for paired data was used to analyze differences between sensitivities at the same specificity.

To detect differences in the discriminatory power of the two methods, the area under the receiver-operating characteristic curve was used. The false positive ratio (1 − specificity) was plotted on the horizontal axis and the true positive ratio (sensitivity) on the vertical axis at various cut points. The area under the generated curves for each diagnostic method represents the discriminatory power of the method. The method of Hanley and McNeil (17) was used to calculate each area as well as the statistical significance of the difference between the two criteria in the overall study group and in different subgroups of patients.

Continuous variables are expressed as mean values ± SD as a measure of dispersion. In comparing the groups of subjects in which only one or the other criterion correctly classified the patients, *t* test and chi-square analyses were used.

Results

Patient characteristics. Clinical variables, exercise performance and angiographic results at the eight participating institutions are listed in Table 1; 2,270 patients fulfilled the entry criteria and were considered for analysis. The mean age was 53 ± 10 years; 78% were men and 54% had typical angina according to the previously defined classification.

Forty-three percent of the patients had ≥0.1-mV ST depression. The average peak heart rate was 133 ± 25 beats/min. Exercise-induced angina was present in 38% of patients and treatment with beta-adrenergic blocking agents (continued at the time of testing) was present in 28%.

At coronary angiography, 57% of patients (range 39% to 85% at different institutions) had at least one 50% narrowing in a major coronary artery, 35% of patients (range 25% to 58%) had two-vessel coronary artery disease and 18% of patients (range 12% to 30%) had triple-vessel or left main coronary artery disease.

Referral bias (Table 1). To estimate factors affecting the decision to perform an angiogram, we examined the percent angiographic referrals for each exercise laboratory. This is the percent of patients who underwent exercise testing and also underwent angiography. The importance of age, gender and symptoms for determining referral at each of the eight institutions can also be evaluated by examining Table 1. The prevalence rate of disease was higher at institutions where the percent of angiographic referrals from the exercise laboratory was higher. This finding is precisely the opposite of what one would expect if exercise test results strongly affected the decision to perform angiography. On the contrary, the institutions with high prevalence rates of disease were more likely to include many men with typical angina pectoris (Table 1). These findings indicate that pretest angiography referral bias was more important than posttest referral (or diagnostic evaluation [workup]) bias.

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Table 2. Comparison of the Two Criteria

	Cut Point	Specificity*	Sensitivity*	p Value
Overall				
ST depression	0.1 mV	64% (62%–66%)	75% (70%–79%)	0.08
ST/HR index	1.43 μV/beats per min	64% (62%–[illegible]%)	78% (73%–82%)	
Peak heart rate <132 beats/min				
ST depression	0.1 mV	60% (57%–64%)	73% (68%–78%)	0.03
ST/HR index	1.75 μV/beats per min	60% (57%–64%)	76% (71%–81%)	
Peak heart rate ≥132 beats/min				
ST depression	0.1 mV	68% (65%–71%)	80% (73%–87%)	1.0
ST/HR index	1.15 μV/beats per min	68% (65%–71%)	80% (73%–87%)	

*Data in parentheses are 95% confidence intervals. HR = heart rate.

Comparison of two criteria (Table 2). Exercise-induced ST depression of 0.1 mV was found to have a specificity of 64% and a sensitivity of 75% for the prediction of triple-vessel or left main coronary artery disease. At the same specificity (64%), the ST/heart rate (HR) index had a sensitivity of 78% ($p = 0.08$) at a cut point equal to 1.43 μV/beats per min.

In the group of patients with a peak heart rate below the median peak heart rate (132 beats/min), 0.1-mV ST depression was found to have a specificity of 60% and a sensitivity of 73%. At the same specificity, the ST/HR index had a higher sensitivity (76%; $p = 0.03$). In those with a peak heart rate equal to or above the median value, specificity and sensitivity of ST depression and ST/HR index were identical (68% and 80%, respectively, $p = 1.0$).

Factors affecting increased accuracy of ST/HR index (Table 3). Among the 401 patients with triple-vessel or left main coronary artery disease, the two criteria were concordant (both negative or both positive) 378 times (94.3%). The ST depression was positive and the ST/HR index negative in 7 patients (1.7%) and the ST/HR index was positive and ST depression negative in 16 patients (4%). When the 7 subjects in whom ST depression was the more accurate indicator were compared with the 16 in whom the ST/HR index was superior were compared by using Student's *t* test and chi-square analyses, only peak heart rate was found to differ significantly between groups. Heart rate averaged 103 beats/min when the ST/HR index was more accurate compared with an average of 156 beats/min when the standard ST depression was more accurate (Table 3). The number of subjects with discordant results is small and the suggestive though not statistically significant difference in the percent taking a beta-receptor antagonist is worthy of note.

Receiver-operating characteristic curve analysis (Table 4). The receiver-operating characteristic curves for the overall data are plotted in Figure 1. For each false positive value, sensitivity was slightly higher for ST/HR index. The area under the curve for ST/HR index was somewhat larger than that for ST depression (0.76 versus 0.74, $p = 0.03$). The value of the area under the curves according to ST depression and ST/HR index are reported in Table 4 for the overall study group and for each of the eight participating institutions. At only one institution (Chicago) was the difference in the area statistically significant.

Discussion

By the classic interpretation, the value of exercise-induced ST segment depression at 0.08 s after the J point is an index of the severity of coronary artery obstruction. The 0.1-mV cut point has been widely used as an imperfect method for distinguishing patients with from those without coronary artery disease (18–24). Unfortunately, its utility is often

Table 3. Univariate Analysis Among 23 Patients With Triple-Vessel or Left Main Coronary Artery Disease With Discordant Results by the Two Methods

	Best Indicator of Disease		
	ST Depression (n = 7)	ST/HR Index (n = 16)	p Value
Mean age (yr)	53 ± 7	55 ± 6	NS
Typical angina (%)	85	69	NS
Mean METs	5.6 ± 1.4	6.5 ± 2.7	NS
Mean peak heart rate (beats/min)	156 ± 8	103 ± 17	0.0001
Exertional angina (%)	57	75	NS
Positive treadmill test (%)	71	69	NS
Beta-blocker use (%)	14	50	NS

METs = metabolic equivalents.

Table 4. Receiver-Operating Characteristic Analysis of Area Under the Curve for Each Center

	ST Depression (%)	ST/HR Index (%)	p Value
Chicago	74	80	0.02
Cleveland	76	79	0.16
Long Beach	70	70	0.88
Basel	65	74	0.52
Budapest	78	80	0.45
Geneva	68	70	0.45
Rotterdam	75	77	0.51
Zurich	65	74	0.27
Overall	74	76	0.03

HR = heart rate.

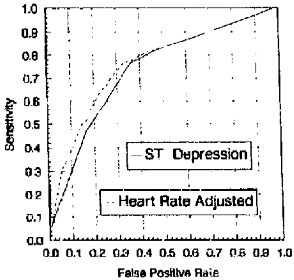

Figure 1. Receiver-operating characteristic curves for the conventional measurement of ST segment depression and the heart rate-adjusted ST segment depression. The end point is angiographic triple-vessel and left main coronary artery disease.

limited by false positive and false negative results (25–28). Because heart rate variations are closely related to the changes in myocardial oxygen demand (29,30), it has been suggested (5) that normalizing the amount of ST depression (index of ischemia) by the corresponding change in heart rate (index of oxygen demand) might increase the accuracy of ST depression in predicting the presence of severe coronary artery disease. As the number of occluded coronary vessels increases, the ratio of oxygen supply to demand decreases and ischemia may occur at a lower heart rate. Therefore, the clinician who sees ST depression at a lower heart rate can suspect more severe coronary artery disease.

Historical perspective (Table 5). To have a historical perspective on the debate, all published reports utilizing heart rate adjustment of exercise results were analyzed. The list of reports was obtained from the bibliographies from two recent reviews (31,32) and from each bibliography of the original reports. Abstracts and letters were excluded from this analysis. Since 1977, 28 original reports have been published (4–10,12,15,33–51) and are listed in Table 5 according to the date of journal acceptance (when stated).

Table 5. Studies of Heart Rate Adjustment of ST Segment Depression

First Author (reference no.)	City	Date of Acceptance or Year of Publication	No. of Patients	Exercise Protocol	Beta-Blocker Use Included	Myocardial Infarction Included	Coronary Artery Disease (%)	3-Vessel or Left Main Disease (%)	Criterion
Simoons (4)	Rotterdam	1977	138	BK	NS	Yes	62	...	ST area/HR
Barenyi (33)	Balatonfured	1979	25	BK	No	Yes	100	36	ST/HR slope
Elamin (5)	Leeds	1980	64	BK	No	Yes	78	23	ST/HR slope
Kardash (34)	Leeds	2/12/82	120	BK	Yes	Yes	89	25	ST/HR slope
Kardash (35)	Leeds	1982	60	BK	Yes	...	97	25	ST/HR slope
Elamin (36)	Leeds	5/18/82	206	BK	Yes	Yes	82	21	ST/HR slope
Silverton (37)	Leeds	10/18/83	22	BK	...	Yes	100	5	ST/HR slope
Kardash (38)	Leeds	10/18/83	46	BK	Yes	Yes	100	28	ST/HR slope
Berenyi (39)	Balatonfured	11/14/83	33	BK	No	Yes	100	36	ST/HR slope
Quyyumi (40)	London	11/22/83	78	BK	Yes	...	73	20	ST/HR slope
Balcon (41)	London	5/15/84	49	BK	Yes	...	86	4	ST/HR slope
Okin (6)	New York	9/18/84	50	TM	Yes	Yes	92	36	ST/HR slope
Ameisen (42)	New York	12/7/84	135	TM	Yes	Yes	70	20	ST/HR slope
Kligfield (43)	New York	5/13/85	35	TM	...	No	57	26	ST/HR slope
Thwaites (44)	London	7/30/85	60	BK	Yes	...	75	18	ST/HR slope
Haraphongse (7)	Edmonton	12/10/85	226	TM	Yes	No	92	27	Sum ST/HR
Finkelhor (45)	Cleveland	12/12/85	64	TM	Yes	Yes	58	9	ST/HR slope
Ameisen (46)	New York	3/11/86	113	TM	Yes	Yes	...	28	ST/HR slope
Okin (47)	New York	1986	150	TM	No	No	...	...	ST/HR slope
Detrano (8)	Cleveland	5/9/86	303	TM	No	No	45	16	ST/HR index
Kligfield (9)	New York	1987	58	TM	Yes	Yes	72	31	ST/HR slope–ST/HR index
Okin (48)	New York	1/6/88	128	TM	Yes	Yes	84	16	ST/HR slope–ST/HR index
Sato (10)	Osaka	3/28/88	142	TM	Yes	No	77	19	ST/HR slope–ST/HR index
Okin (49)	New York	7/18/88	62	TM	No	No	70	20	ST/HR slope–ST/HR index
Kligfield (50)	New York	9/27/88	300	TM	Yes	Yes	33	14	ST/HR slope–ST/HR index
Bugiardini (51)	Bologna	4/10/89	42	BK	No	No	100	24	ST/HR slope
Deckers (15)	Rotterdam	6/14/89	345	BK	Yes	No	49	16	ST/HR index–ST/HR area
Lachterman (12)	Long Beach	1990	328	TM	Yes	Yes	36	20	ST/HR index
Bobbio (present study)	Multicenter		2,270	BK/TM	Yes	No	58	18	ST/HR index

... = not stated; abbreviations as in Tables 1 and 2.

The Leeds group (5,34–38) found a perfect separation of single-, double- and triple-vessel coronary artery disease using a variation of the previous approach in six consecutive studies. However, two investigations (40,41) at two different institutions in London were not able to reproduce these results. The Cornell group (6,42,43,46,47) and others (7,45) showed improved accuracy using the same approach, although some false positive and false negative results were encountered.

In relatively small groups of patients, the Cornell group compared the ST/heart rate (HR) index, used in the present investigation, with their variation of the Leeds method (43,46). The ST/HR index was almost as accurate as the ST/HR slope for predicting any angiographic narrowing in one of their studies (9) but was significantly inferior for predicting triple-vessel or left main coronary artery disease in the other (45). These investigators recently reported (50) significant superiority of the ST/HR index over standard ST depression for predicting any significant angiographic disease. However, Lachterman et al. (12) recently found no significant difference in accuracy when the ST/HR index and standard ST depression were used to predict any significant coronary artery disease in 328 subjects undergoing cardiac catheterization.

The ST/HR index method as used in the present study has the advantage of simplicity of calculation, does not require a computer, can be used for screening purposes and can be applied to large groups of patients for retrospective analysis of available data (52). However, the ST/HR slope method does present certain theoretic advantages and it is possible that significant improvement over the ST/HR index could be achieved with the slope method. In light of the scanty comparative data for the slope and index methods (12,45) and the contradictions between the results of Lachterman et al. (12) and the Cornell group (9,45), no conclusive proof of this theoretic advantage is available.

Referral bias. In all studies involving coronary angiography as a standard to define disease, the bias incurred in the referral process can be problematic. This bias can be divided into two types: *pretest referral bias* involving age, gender, symptoms and risk factors and *posttest referral bias* (or workup bias) involving stress test results (53). To reduce posttest bias, exercise tests in the Cleveland group were performed for research purposes and the results were not used in the decision to perform angiography. Despite the resulting reduction in the amount of workup bias, the Cleveland results were similar to the results at the other seven institutions where workup bias was presumably more important.

Further assessment of the effect of referral bias can be achieved by examining the referral patterns from the exercise laboratories. In Table 1, we have displayed the percent of angiographic referrals at each laboratory. If workup bias was an important determinant of the difference in accuracies, one would expect to see corresponding differences in the areas under the receiver-operating characteristic curves for the two methods. No such differences were found. We therefore see no reason to consider referral bias as an important determinant of the apparent failure of the ST/HR index in our study. Furthermore, a recent meta-analysis (54), treating 147 consecutive published reports that compared exercise-induced ST depression with coronary angiography, found no significant effect of referral bias on test accuracy when controlling for 28 other variables.

Comparison with previous studies. Past studies have restricted the application of the heart rate-adjusted ST depression to patients at only one laboratory. In the present study, 2,270 patients from eight institutions in three countries were analyzed. Data were collected according to an international collaborative protocol. In most of the studies listed in Table 5, patients were selected according to several characteristics that would reduce the number of false positive and false negative findings (the so-called avoidance of a limited challenge group [53]). This factor may partially account for the disparity between the results of these studies and our own.

Limitations. Many cardiologists consider the slope of ST segment depression as well as its magnitude. Upsloping depressions are assigned less diagnostic importance than that of those that are horizontal or downsloping. Had we used this modification to conventional ST depression, its accuracy might have improved sufficiently to make it superior to the ST/HR index.

The comparison we made involves the case of predicting triple vessel or left main coronary artery disease. Our results for predicting coronary artery disease in one or two vessels are similar and will be published soon (55).

Conclusions. As shown by the analysis of discordant cases, the ST/HR index performs better at a lower peak heart rate. From the clinical point of view, a small ST depression at a low heart rate could be misleadingly interpreted as negative, thus raising the false negative rate. By adjusting the small ST depression at low heart rates, the ST/HR index could reach the cut point of 1.43 μV/beats per min. Accordingly, the superior performance of the ST/HR index in patients receiving beta-blocker therapy (Table 3) could be ascribed to the lower heart rate reached during exercise. The differences in accuracy of the ST/HR index found at different institutions could be partially explained by the different heart rates achieved. Thus, the routine use of heart rate adjustment of exercise-induced ST depression provides only minimal improvement in test accuracy. However, this method may be used for individuals who fail to achieve the anticipated increase in heart rate.

The editorial assistance of Barbara Vaitovas and Jeanette Phillips is deeply appreciated.

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