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A Reappraisal of Exercise Electrocardiographic Indexes of the Severity of Ischemic Heart Disease: Angiographic and Scintigraphic Correlates

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Objectives. **We explored how the exercise electrocardiographic (ECG) indexes generally presumed to signify severe ischemic heart disease (IHD) correlate with coronary angiographic and scintigraphic myocardial perfusion findings.**

Background. **In exercise testing, it is generally assumed that the early onset of ST segment depression and its occurrence at a low rate–pressure product (ischemic threshold); the amount of maximal ST segment depression; and a horizontal or downsloping ST segment and its prolonged recovery after exercise signify more severe IHD. However, the relation of these indexes to coronary angiographic and exercise myocardial perfusion findings in patients with IHD is unclear.**

Methods. **We prospectively carried out a symptom-limited 12-lead Bruce protocol thallium-201 single-photon emission computed tomographic (SPECT) exercise test in 66 consecutive subjects with stable angina, ≥70% stenosis of at least one coronary artery, normal rest ECG and left ventricular wall motion and a prior positive exercise ECG. The above ECG indexes, vessel disease (VD), a VD score and the quantitative thallium-SPECT measures of the extent, maximal deficit and redistribution gradient of the perfusion abnormality were characterized.**

Results. **Maximal ST segment depression could not differentiate the number of diseased vessels; was not related to VD score, maximal thallium deficit or redistribution gradient; but was related to the extent of perfusion abnormality ($r = 0.29$, 95% confidence interval [CI] 0.08 to 0.52, $p = 0.02$). Time of onset of ST segment depression correlated inversely only with VD ($r = -0.22$, 95% CI −0.44 to −0.05, $p < 0.05$), whereas the ischemic threshold had low inverse correlation only with VD score ($r = -0.25$, 95% CI −0.47 to −0.01, $p < 0.05$) and the redistribution gradient ($r = -0.33$, 95% CI −0.53 to −0.10, $p < 0.01$). A horizontal or downsloping compared with an upsloping ST segment did not demonstrate more severe angiographic and scintigraphic disease. Recovery time did not correlate with angiographic and scintigraphic findings, and correlations between angiographic and scintigraphic findings were also low or absent.**

Conclusions. **In this homogeneous study group, the exercise ECG indexes did not necessarily signify more severe IHD by angiographic and scintigraphic criteria. Lack of concordance between the exercise ECG, angiography and myocardial scintigraphy suggests that these diagnostic modalities examine different facets of myocardial ischemia, underscoring the need for caution in the interpretation of their results.**

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In exercise testing, a number of electrocardiographic (ECG) indexes are presumed to be associated with the presence of severe ischemic heart disease (IHD). These include an early-onset positive exercise test, a low product of heart rate and systolic blood pressure at the onset of positivity, the amount of ST segment depression (STD), the number of ECG leads exhibiting positivity and a downsloping ST segment at peak exercise and a longer duration of ECG positivity after exercise (1–4). However, these assumptions are based on older, generally retrospective studies whose focus has been the sensitivity and predictive power of the exercise ECG as a diagnostic test, with the reference standard for significant disease being 50% or 70% coronary artery diameter stenosis on angiography. By design, these studies have included subjects with both false positive and false negative exercise ECG tests (2–8). Because false positive exercise tests are usually not strongly positive and because false negative tests tend to be associated with less severe disease (9,10), inclusion of such patients in a study cohort would suggest that more positive tests must signify more severe disease. The significance of ECG changes may have been further blunted by stopping the exercise test at an arbitrary limit of STD or by the presence of previous myocardial infarction or rest ECG abnormalities (2,3,6,7).

We therefore prospectively explored, in a well characterized group of patients with stable angina with both a positive exercise ECG and significant angiographic coronary artery disease (CAD) but without myocardial infarction, left ventricular dysfunction or rest ECG abnormalities, how the exercise

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Abbreviations and Acronyms

CAD = coronary artery disease
CI = confidence interval
ECG = electrocardiogram, electrocardiographic
IHD = ischemic heart disease
METs = metabolic equivalents
MSTD = maximal ST segment depression
SPECT = single-photon emission computed tomography (tomographic)
STD = ST segment depression
VD = vessel disease

ECG indexes generally presumed to be associated with severe IHD correlate with angiographic and scintigraphic myocardial perfusion imaging findings.

Methods

Patients. Consecutive patients with stable angina undergoing elective coronary arteriography and found to have ≥70% stenosis of at least one major coronary artery were recruited if they also had 1) no previous history of myocardial infarction, defined as creatine kinase greater than or equal to twice the upper normal limit; 2) a normal rest ECG with the exception of minor, nonspecific T wave abnormality; 3) a previously positive exercise test (≥1-mm STD 80 ms after the J point); and 4) normal wall motion on left ventriculography (minor or questionable regional hypokinesia was allowed). Patients with left main coronary artery stenosis ≥50% were excluded for safety reasons. With consecutive recruitment of eligible patients, twice as many subjects with single-vessel disease (≥70% stenosis) were initially studied. Therefore, to strike as even as possible a balance with patients with multivessel disease, subsequent recruitment continued to be weighted 2:1 in favor of those with two- and three-vessel disease (60 to 70 patients in all). The study protocol was approved by the hospital's institutional review board, and written informed consent was obtained.

Exercise protocol. Within 1 month of coronary arteriography, patients underwent a symptom-limited exercise treadmill test using the standard Bruce protocol and thallium-201 single-photon emission computed tomographic (SPECT) imaging. All tests were performed in midmorning in the fasting state. Beta-adrenergic blocking agents and calcium antagonists were stopped at least 48 h and nitrates at least 12 h before testing. No patients were taking digitalis. The cardiologist supervising the exercise test was unaware of the patient's coronary angiographic findings. All exercise tests were performed on a Q65 treadmill linked to a Q4000 monitor (Quinton Instrument Co.). The ECG was continuously monitored. A standard 12-lead ECG was taken in the supine and standing positions and then every 30 s during exercise and recovery. Each time, both an averaged and a raw-data ECG was obtained. The arterial blood pressure was taken with a mercury sphygmomanometer every 2 min until peak exercise and then three times during recovery. Indications for stopping the exercise test were uncomfortable dyspnea or angina, a drop in blood pressure >10 mm Hg or a serious arrhythmia. In only three of the subjects did one of these last two events occur. One minute before the anticipated end of exercise, 3.0 mCi (111 MBq) of thallium-201 was injected intravenously and flushed with saline. The patient recovered in the sitting position for a maximum of 5 min and was then taken by wheelchair within 5 min to the scintigraphic imaging camera.

The exercise test was considered positive at first appearance of 1-mm STD 80 ms after the J point, compared with the rest ECG taken in the standing position just before exercise. The raw data and averaged tracings were examined for consistency, requiring three consecutive beats with similar findings. The time of onset of exercise test positivity and the corresponding heart rate–systolic blood pressure product or ischemic threshold were noted. Maximal ST segment depression (MSTD) was noted on raw data and averaged tracings taken just before the end of exercise. All leads exhibiting the criteria of positivity at the end of exercise were noted, as was the configuration of the slope—up, horizontal or down—in the lead with MSTD. Recovery time was the time from the end of exercise to the final appearance of 1-mm STD. Electrocardiographic recovery time analysis was truncated at 5 min because of the need to proceed with the scintigraphic imaging protocol. All exercise tracings were analyzed in blinded manner and independently by two examiners, who resolved differences by consensus.

Coronary angiography. Coronary arteriography and left ventriculography were performed according to standard techniques. Coronary arteriograms were evaluated independently by two experienced observers, using calipers, who had no knowledge of the other clinical data, and any differences were resolved by consensus. Subjects were classified as having one-, two- and three-vessel disease according to the Coronary Artery Surgery Study criteria of 70% stenosis of the major coronary arteries (11). In addition, a vessel disease (VD) score was assigned depending on the importance of the artery and the location of the ≥70% stenosis, as previously described (12). Because no consensus exists regarding the status of stenoses of 50%, all data were also analyzed considering a stenosis to be significant at 50%.

Thallium scintigraphy. A 5-min planar anterior view was first obtained within 10 min of injection of thallium-201, followed by SPECT imaging performed on a large field-of-view, single-head rotation gamma camera with 0.37-in. thick (0.94-cm) sodium iodide crystal and 75 photomultiplier tubes (Siemens Orbiter) equipped with a low energy, all-purpose, parallel-hole collimator. The system was linked to a Siemens Microdelta computer. A 20% energy window centered on the 80-keV X-ray peak and a 10% window centered on the 167-keV gamma-ray peak were used. Sixty-four 20-s projections were acquired over a 180° arc, extending from the 45° right anterior oblique to the 45° left posterior position using a circular orbit. Data were stored in a 64 × 64, 16-bit (word) matrix. Field nonuniformity and center of rotation offset

corrections were performed before reconstruction. A Butterworth filter with a cutoff of 0.4 and an order of 5.0 was used for processing the raw data after prereconstruction interslice averaging using a 0.25, 0.50, 0.25 weighting array. Sections were reconstructed in short, vertical long and horizontal long axes.

Redistribution thallium-201 imaging was performed 4 h after injection using the same variables of acquisition and reconstruction. Rest thallium-201 images were obtained 15 min after rest reinjection of thallium-201 (1 mCi if within 24 h or 2.5 mCi otherwise) in patients with fixed or only partially reversible myocardial defects on redistribution imaging. All rest studies were obtained within 7 days of exercise imaging. After reconstruction, all images were checked and realigned, if necessary, for appropriate registration of stress, redistribution and rest thallium-201 images in each plane. Two-dimensional polar map displays representing extent and severity of disease were generated for the initial tomograms and delayed tomograms using commercially available software (13,14).

Scintigraphic data analysis. One-pixel thick (6 mm) contiguous slices were added together in the three axes to obtain two-pixel thick (12 mm) slices. After visual inspection of myocardial perfusion defects, the severity of disease was characterized in two ways: 1) as the ischemic to normal wall ratio obtained from circumferential profiles on the slice showing the most severe perfusion defect; and 2) as the improvement of the most severe deficit from the stress study to the delayed study, expressed in percent and referred to as the redistribution gradient. The extent of the perfusion abnormality was evaluated by the percentage of abnormal myocardium on the extent polar map display. These methods of measuring the extent and severity of myocardial ischemia, except for the redistribution gradient, have been previously validated (13,14). All scintigrams were evaluated by a single experienced specialist in cardiac nuclear medicine who was unaware of the patients' other clinical data. In all cases, thallium-201 heart to lung uptake ratios were assessed from stress and redistribution planar views to rule out any possible underestimation of scintigraphic disease severity due to diffuse multivessel disease. An example of the images and data generated by one of the study patients is shown in Figure 1.

Statistical analysis. All data are expressed as mean value ± SD. The Spearman rank correlation coefficient was used, as the relation between variables was not linear, and was expressed with 95% confidence interval (CI). Multivariate regression analysis of the ECG indexes of severity, examining for relations with angiographic and scintigraphic indices of severity, was first performed. Comparisons were made using analysis of variance or the Kruskall-Wallis test, as appropriate. The Fisher exact test was used to analyze differences in proportions. A p value <0.05 was considered statistically significant.

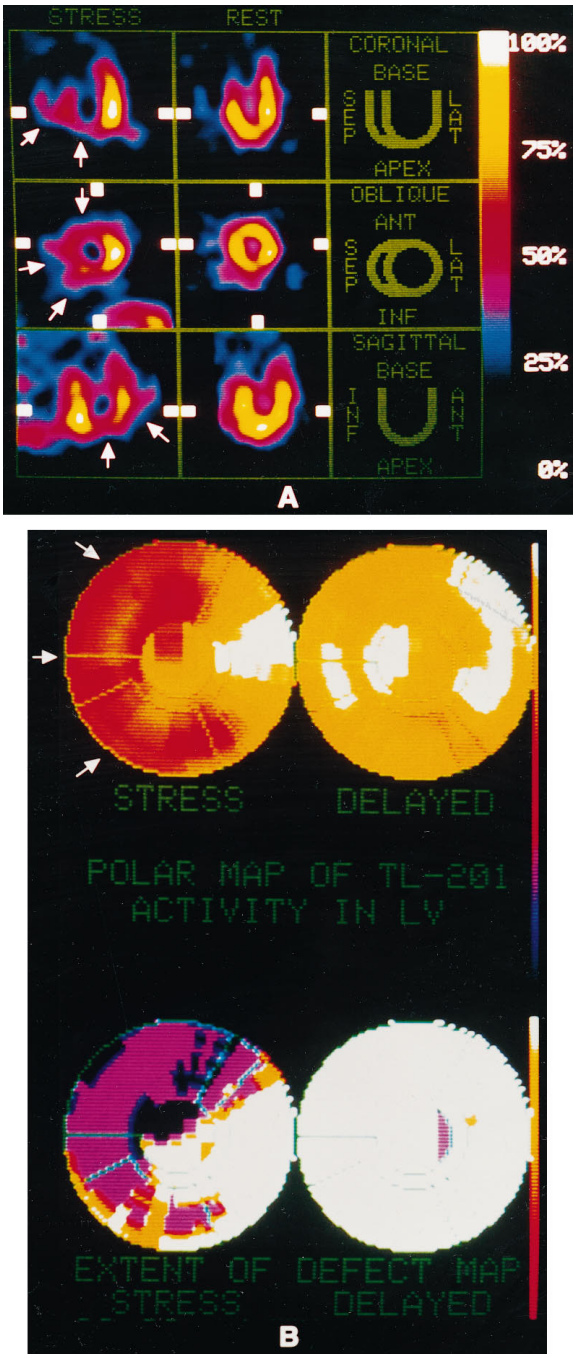

Figure 1. Example of an exercise (stress) and redistribution (rest) thallium-201 (TL-201) SPECT imaging study. **A,** Representative midventricular slices are shown on horizontal long (coronal), short (oblique) and vertical long (sagittal) axes (**top to bottom**). Reversible anterior (ANT), apical (APEX), septal (SEP) and inferoseptal (INF-SEP) perfusion defects (**arrows**) can be clearly seen. **B,** Polar map or bull's-eye image of the relative distribution of thallium-201 in the myocardium of the left ventricule (LV). The exercise (STRESS) map (**top left**) shows the defect as **red area** in the anterior, apical, septal and inferoseptal regions (**arrows**). On the extent map (**bottom**), hypoperfused areas, compared with a data base of normal subjects, are shown as **purple** and **black areas**. Normal myocardium is displayed as **white area**. The total extent of the defect on the extent map (**bottom left**) is 57% of the left ventricle. Redistribution (DELAYED) polar maps (**top and bottom right**) are within the normal range. INF = inferior; LAT = lateral.

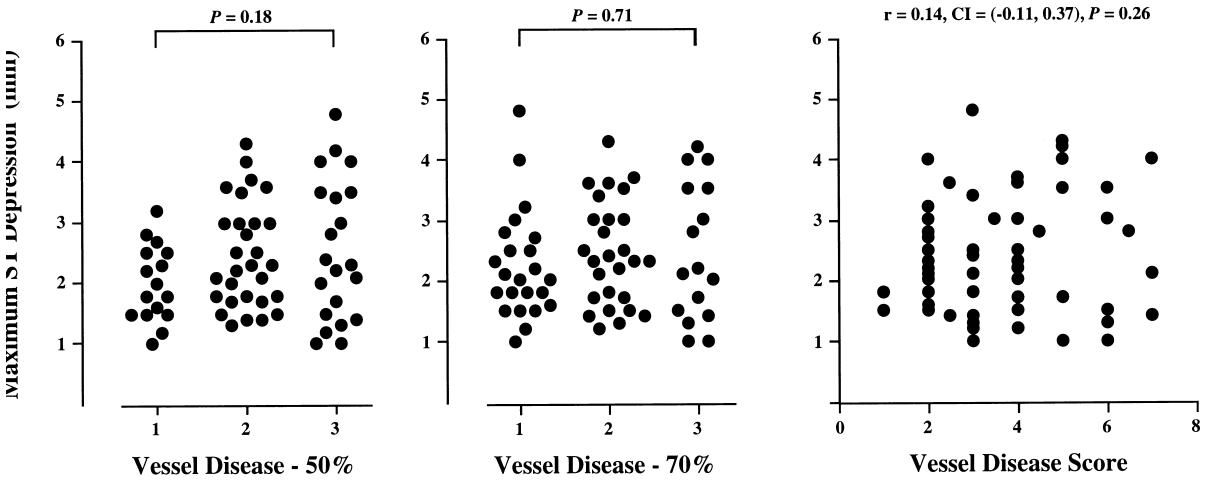

Figure 2. Relation of maximal exercise-induced STD with the number of diseased vessels (using both the 50% and 70% stenosis definitions of VD) and with the VD score (70% stenosis definition of vessel disease). MSTD did not discriminate the severity of VD. No correlation was found between MSTD and VD score.

Results

Clinical findings. Sixty men and six women (59 ± 9 years old) were studied: 23 had one-vessel disease, 27 had two-vessel disease and 16 had three-vessel disease. Vessel disease score was 3.6 ± 1.6. When VD was defined as 50% stenosis, 16 had one-vessel disease, 29 had two-vessel disease and 21 had three-vessel disease, and the VD score was 4.0 ± 1.5. Only one subject had previous coronary artery (double) bypass graft surgery, and both of his grafts were occluded. Within 3 months of the study protocol, 35 subjects (53%) underwent bypass surgery and 17 (26%) had coronary angioplasty. Exercise work load achieved was 8.2 ± 2.2 metabolic equivalents (METs). MSTD was 2.4 ± 0.9 mm. The slope of this depression was upward in 16 (24%), horizontal in 44 (67%) and downward in 6 (9%) subjects. The number of positive leads at peak exercise was 5.9 ± 1.8. The duration of exercise positivity from initial onset of 1-mm STD to peak exercise was 3.1 ± 1.8 min. Recovery time was 3.1 ± 1.8 min.

Correlation of magnitude and extent of STD with angiographic and scintigraphic variables. The relation between one-, two- and three-vessel disease and MSTD both at 50% and 70% stenosis is shown in Figure 2. MSTD was unable to discriminate the number of diseased vessels. Unless otherwise stated, all subsequent analyses will consider VD at 70% stenosis. There was no correlation between MSTD and VD score (Fig. 2), nor between the number of leads exhibiting positivity at peak exercise and VD or VD score. However, there was a relation between MSTD and the number of positive leads ($r = 0.65$, 95% CI 0.49 to 0.77, $p < 0.001$).

In Figure 3, MSTD is plotted against the corresponding extent of the thallium perfusion abnormality, expressed as the percentage of abnormal myocardium on the extent polar map display. The correlation, although significant, was low. No relation was found between MSTD and the most severe perfusion deficit, nor with the redistribution gradient. The only scintigraphic variable to correlate with the number of positive ECG leads at peak exercise was the maximal deficit, and this correlation was low ($r = 0.29$, 95% CI 0.06 to 0.50, $p = 0.02$).

Correlations of exercise test positivity onset with angiographic and scintigraphic variables. The correlations between the onset of 1-mm STD in terms of time, heart rate and rate–pressure product or ischemic threshold and VD or VD score are displayed in Table 1. The earlier the exercise test became positive, the greater the VD; however, this negative correlation was low and none was found between the time of onset of exercise positivity and the VD score. There was no correlation between the heart rate at the onset of positivity and angiographic findings. The ischemic threshold did not corre-

Figure 3. Relation of the extent of the thallium perfusion abnormality with maximal exercise-induced STD. The correlation between these two variables, although significant, was low.

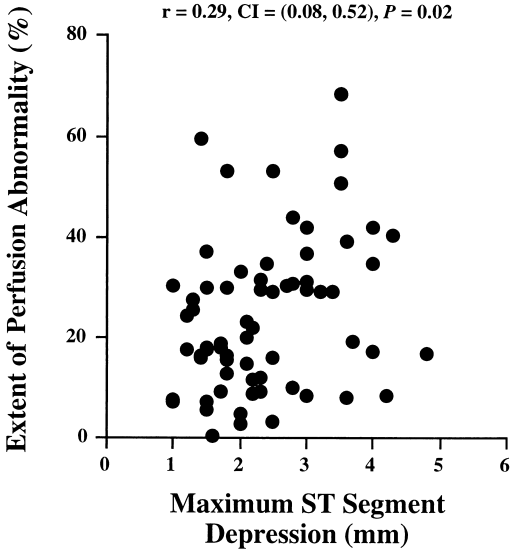

Table 1. Correlations of Exercise Electrocardiographic Positivity Onset, Recovery Time and Metabolic Equivalents With Angiographic and Scintigraphic Variables

	VD [r (95% CI)]	VD Score [r (95% CI)]	Extent of Perfusion Abnormality [r (95% CI)]	Max Perfusion Deficit [r (95% CI)]	Redistribution Gradient [r (95% CI)]
Time at 1st +	−0.22 (−0.44 to −0.05)*	−0.16 (−0.39 to 0.08)	0.05 (−0.19 to 0.29)	0.12 (−0.12 to 0.35)	−0.06 (−0.30 to 0.18)
Heart rate at 1st +	−0.13 (−0.36 to 0.12)	−0.14 (−0.37 to 0.11)	0.01 (−0.23 to 0.25)	0.10 (−0.14 to 0.34)	−0.16 (−0.39 to 0.08)
Ischemic threshold	−0.20 (−0.43 to 0.04)	−0.25 (−0.47 to −0.01)*	−0.06 (−0.30 to 0.18)	0.04 (−0.20 to 0.28)	−0.33 (−0.53 to 0.10)†
Recovery time	0.04 (−0.21 to 0.28)	0.06 (−0.18 to 0.30)	0.15 (−0.10 to 0.38)	0.20 (−0.05 to 0.42)	0.21 (−0.04 to 0.43)
METs	−0.44 (−0.62 to −0.22)†	−0.36 (−0.56 to −0.13)†	0.00 (−0.24 to 0.24)	0.06 (−0.18 to 0.30)	−0.03 (−0.27 to 0.21)

*$p < 0.05$. †$p < 0.01$. CI = confidence interval; Ischemic threshold = rate–pressure product at first appearance of exercise electrocardiographic (ECG) positivity; Max = maximal; METs = metabolic equivalents; r = correlation coefficient; Recovery time = time from end of exercise to disappearance of ECG positivity; VD = vessel disease; 1st + = point during exercise test where positivity (1-mm ST segment depression) first appeared.

late with the number of diseased vessels, but did so with the VD score; the lower the ischemic threshold, the greater the VD score, but again this negative correlation was low.

No correlation of any of these indexes with the extent of the perfusion abnormality or with the maximal perfusion deficit was present (Table 1). Only between the ischemic threshold and the redistribution gradient was a low inverse relation found ($r = -0.33$, 95% CI −0.53 to −0.10, $p = 0.008$); the lower the ischemic threshold, the greater the redistribution gradient.

Correlations of exercise test recovery time. No relation was found between recovery time and any of the angiographic and scintigraphic variables examined (Table 1). Recovery time did correlate with the amount of time during the exercise test that the ECG was positive ($r = 0.51$, 95% CI 0.30 to 0.67, $p < 0.001$), and the relations of both these variables with MSTD were moderately high ($r = 0.49$, 95% CI 0.29 to 0.66, $p < 0.001$ and $r = 0.54$, 95% CI 0.34 to 0.69, $p < 0.001$, respectively).

Correlations of work load achieved. The METs of exercise accomplished correlated inversely with VD and VD score; more METs were therefore associated with less severe angiographic disease; however, there was no relation of METs with any of the scintigraphic indexes (Table 1). There was a significant but low direct relation between METs and the time of onset of exercise positivity ($r = 0.25$, 95% CI 0.01 to 0.47, $p < 0.05$). No relation was found between METs, on the one hand, and MSTD, the ischemic threshold or the recovery time, on the other.

Correlations of slope of ST segment depression (Table 2). Downsloping MSTD was associated with a lower heart rate at first appearance of exercise ECG positivity compared with upsloping and horizontal STD. Also, the ischemic threshold tended to be lower, MSTD was greater and recovery time tended to be longer with a downsloping ST segment. However, the configuration of the slope permitted no clear, clinically pertinent inference as to the severity of the disease by any of the angiographic and scintigraphic criteria examined.

Correlations of angiographic and scintigraphic variables. Table 3 shows that the VD score had a significant but low correlation with the extent of the perfusion abnormality, whereas VD had none. No significant relation was present between VD or VD score and the maximal perfusion deficit or the redistribution gradient.

Correlations with VD defined as 50% stenosis. When the data were reanalyzed with this definition of VD, there were no significant changes in any of the earlier results.

Table 2. Exercise Electrocardiographic, Angiographic and Scintigraphic Correlations of Slope of Maximal Exercise-Induced ST Segment Depression

	Slope of Max ST Segment Depression			
	Upsloping (n = 16)	Horizontal (n = 44)	Downsloping (n = 6)	p Value
Time at 1st + (min)	3.0 ± 2.2	3.5 ± 2.1	3.5 ± 2.1	0.76
Heart rate at 1st + (beats/min)	107 ± 10	105 ± 13	92 ± 12	0.03*
Ischemic threshold ($\times 10^{-3}$)	17.5 ± 2.1	16.2 ± 3.3	14.1 ± 2.9	0.07
No. of pos leads at peak ex	5.4 ± 1.8	6.1 ± 1.8	5.8 ± 1.5	0.38
Max ST segment depression (mm)	1.9 ± 0.7	2.5 ± 0.9	2.9 ± 1.1	0.06
Recovery time (min)	2.4 ± 1.9	3.4 ± 1.8	3.5 ± 1.8	0.21
VD	1.9 ± 0.7	1.9 ± 0.8	1.7 ± 0.8	0.73
VD score	3.3 ± 1.4	3.6 ± 1.6	3.8 ± 1.7	0.75
Extent of perfusion abnormality (%)	27.9 ± 18.4	22.7 ± 14.7	25.3 ± 9.5	0.30
Max perfusion deficit (%)	48.5 ± 8.7	47.5 ± 10.8	43.3 ± 13.3	0.60
Redistribution gradient (%)	26.9 ± 10.5	27.0 ± 11.4	25.5 ± 12.0	0.95

*Downsloping versus upsloping and horizontal. Data presented are mean value ± SD. ex = exercise; pos = positive; other abbreviations as in Table 1.

Table 3. Correlations of Angiographic and Scintigraphic Variables

	VD [r (95% CI)]	VD Score [r (95% CI)]
Extent of perfusion abnormality	0.16 (−0.08–0.39)	0.31 (0.07–0.45)*
Max perfusion deficit	0.01 (−0.24–0.25)	0.00 (−0.24–0.24)
Redistribution gradient	0.21 (−0.03–0.43)	0.21 (−0.03–0.43)

*$p < 0.05$. Abbreviations as in Table 1.

Discussion

This study, undertaken in a homogeneous group of patients with stable angina without a previous infarction and with a normal rest ECG and left ventricular function, a positive exercise ECG and significant CAD, suggests that the concordance of the ECG indices presumed to indicate severe IHD with angiographic and myocardial perfusion findings is generally poor. None of the following variables showed a high correlation with VD or VD score or with scintigraphic perfusion imaging measures of severity and extent of ischemia: time, heart rate or rate–pressure product at the onset of exercise positivity, amount of STD, ST segment slope configuration, number of positive leads at peak exercise or duration of recovery time. More often such a correlation was absent and, when present, it was low.

ST segment depression. What, then, does exercise-induced STD signify? Assumed to indicate subendocardial ischemia (15) and dependent on heart rate, blood pressure and contractility (16), its electrophysiologic or biochemical basis is not well defined. Animal and human experimental studies have shown links between ST segment change and flow, metabolism and intracoronary pressure-derived indexes (17–20). Myocardial SPECT perfusion imaging might have been expected to correlate with the amount of STD in terms of the degree of hypoperfusion or its extent, or both. However, we found no correlation of STD with the scintigraphic indexes of severity (the maximal deficit and the redistribution gradient) and a significant, albeit low, correlation with the extent of the perfusion imaging abnormality. This could be a technical limitation of SPECT, which might lack the resolution necessary to correlate the ST segment with reduced flow. It could also be that the STD recorded on surface ECG leads is the resultant of a complex barrage of intramyocardial ischemic signals and might also depend on the individual's heart–chest wall interface. Exercise-induced STD would therefore be subject to the unpredictable play of attenuation and amplification. Finally, there may be no a priori reason to assume a strong concordance between the pathophysiologic processes responsible for STD and the mechanisms responsible for myocardial thallium uptake abnormalities any more than with the severity and extent of angiographic abnormalities.

In contrast to the poor concordance of exercise ECG indexes with angiographic and scintigraphic variables, there was a moderately high correlation of STD with the duration of STD both during exercise and recovery, as previously shown (12). The longer the ischemia was present during exercise, the more depressed tended to be the ST segment at peak exercise and the longer it tended to take to recover, suggesting that the perturbation of the ST segment during exercise and recovery may depend more on the intensity of ischemia elicited by exercise than on the severity of IHD defined angiographically or scintigraphically.

Early onset positivity/ischemic threshold. The low or absent correlation between the severity of IHD and the earliness of onset of a positive exercise ECG or its appearance at a lower ischemic threshold might also not be surprising. The positive exercise ECG may only be indicating that an ischemic "signal" is being emitted from a region of myocardium with a low coronary artery reserve. The strength of the signal, its precocity or its threshold might not allow any definite inference as to the extent of the ischemic myocardium.

Angiographic and scintigraphic correlations. The correlation between angiographic and scintigraphic criteria of IHD severity was also found to be absent or low. This might not be unexpected, as there can be a discordance between anatomic severity of IHD and coronary artery reserve evaluated by maximal possible exercise and, on theoretic grounds, perfusion imaging might be expected to better reflect the latter (21). On the one hand, diffuse endothelial dysfunction caused by the atherosclerotic process could result in an underestimation by angiography of the severity of exercise-induced myocardial ischemia (22); on the other hand, collateral flow could attenuate the repercussions of severe angiographic disease, and thus angiography might overestimate the extent of the ischemic substrate (23). However, exercise scintigraphy could underestimate the extent of the ischemic substrate if cardiac factors like angina or dyspnea or extracardiac factors like fatigue prevented thallium abnormalities from appearing in those myocardial regions with a higher threshold for ischemia, albeit subserved by coronary arteries with significant stenosis (24). Thus, the lack of correlation of angiography and scintigraphy might be anticipated even though it is accepted that exercise scintigraphy has excellent sensitivity for the detection of significant CAD (25).

Comparison with other studies. Previous studies have established that the sensitivity, specificity and predictive power of exercise ECG testing for the presence and severity of IHD increases the more the test is positive in terms of MSTD, downsloping STD, number of leads, precocity and longer recovery time (2–7). These studies have been generally retrospective and have usually included both patients without significant disease (false positive exercise tests) and patients with significant disease (defined by 50% or 70% angiographic stenosis) but negative tests. This approach, although useful for establishing norms of diagnostic sensitivity and prediction, has contributed less to our understanding of what perturbed exercise ECG, scintigraphic and angiographic variables may signify and how they correlate in patients who a priori have both a positive exercise test and significant CAD. It is important to emphasize these methodologic distinctions between this study and most previous ones. Because our objective was to better understand the correlations of ECG indexes of IHD severity with scintigraphic and angiographic data in patients

with IHD, we designed this study to exclude subjects with false positive exercise tests and those with significant CAD but negative exercise tests.

A few previous studies have suggested that the correlation between these diagnostic modalities may be poorer than is generally assumed (24,26–28). Their limitations as well as those of other studies correlating exercise with scintigraphy have been their retrospective design (24,26,27,29), use of a limited number of ECG leads during exercise (26), nonsystematic or biased use of scintigraphy or angiography (8,24,27,28) and use of planar rather than tomographic imaging, generally without quantification (8,24,26–28). In a previous, smaller study, we were unable to find a correlation between exercise ECG and angiographic indexes of IHD severity (12).

The strengths of the present study are its prospective design, consecutive recruitment, comprehensive exercise ECG characterization and systematic use of coronary arteriography and quantitative SPECT analysis. In addition, the selection criteria removed the potentially confounding factors of medications and rest ECG and left ventricular wall motion abnormalities on the ST segment during exercise and strengthened the interpretation of the thallium perfusion studies by ensuring that little or no scarred myocardium would be present.

Potential study limitations. The present study patients constitute a relatively selected group, and findings might not necessarily be extrapolated to patients with other clinical characteristics. Any biases were those deliberately imposed by the selection criteria and the recruitment of subjects from a consecutive list referred for coronary arteriography. Women and men could be analyzed together because they all had angina, positive ECG exercise tests and significant CAD. Study subjects had a normal rest ECG and wall motion, no previous myocardial infarction and absence of significant left main CAD. They had to be stable and able to exercise and tolerate antianginal medication suspension. Although there were comparable numbers of patients with one-, two- and three-vessel disease using the 50% stenosis criteria, patients with three-vessel disease with 70% stenosis were slightly less well represented because such patients without a previous infarction and a normal rest ECG are found less frequently. Therefore, in the spectrum of chronic IHD, the patients in this study may have had a relatively good prognosis and not the most severe coronary insufficiency. In contrast, the recruitment of patients with a previously positive exercise ECG undergoing coronary arteriography may have resulted in the inclusion of patients more likely to have more severe angina and more perturbed exercise test results such as earlier positivity, more severe or extensive STD and a longer recovery time. In support of this, over half the patients had subsequent coronary artery bypass graft surgery and a quarter underwent coronary angioplasty. These elements reinforce the pathophysiologic and clinical pertinence of these findings by highlighting the surprisingly low correlations of exercise ECG, angiographic and scintigraphic indexes of IHD severity.

This study did not examine more complex ECG variables that have been proposed, such as linear regression analysis of the heart rate–related change in STD (30) or a score integrating ST segment amplitude and slope changes (31). Because the difficulty of using them in routine clinical practice, these have not been shown to be clearly superior to the more readily available parameters of STD (32).

The estimation of angiographic CAD severity was performed by experienced observers in blinded manner using caliper measurements rather than state-of-the-art quantitative computerized analysis. However, the findings are probably no less clinically pertinent because, in practice, angiographic disease is usually evaluated and clinical decisions made on the basis of such visual methods. This is consistent with the purpose of the study, which was to correlate such perceived angiographic disease with the other diagnostic indices.

Conclusions. In this selected patient group, a strongly positive exercise ECG, an early or low ischemic threshold, horizontal or downsloping STD and a prolonged recovery time did not necessarily signify more severe IHD both by angiographic and scintigraphic criteria. These findings raise questions regarding other mechanisms contributing to STD and its recovery in exercise testing in patients with IHD. The low, at best, correlations between exercise ECG and angiography, exercise ECG and scintigraphy, and angiography and scintigraphy underscore the difficulty of assimilating myocardial ischemia to a single reference standard and suggest instead that these diagnostic modalities may be examining different facets of a complex phenomenon.

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