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Hemodynamic, Angiographic and Scintigraphic Correlates of Positive Exercise Electrocardiograms: Emphasis on Strongly Positive Exercise Electrocardiograms

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The results of treadmill exercise electrocardiograms were analyzed in 179 patients with coronary artery disease (≥ 50% diameter narrowing of one or more vessels). Exercise thallium-201 images were available in 141 of these patients. The exercise electrocardiograms were strongly positive in 51 patients, mildly positive (1 to 1.9 mm ST depression) in 28 patients, falsely negative in 23 patients and uninterpretable in 77 patients.

The degree of exercise-induced ST depression did not correlate with left ventricular function, extent of coronary artery disease, exercise heart rates and rate-pressure product and extent of exercise-induced thallium-201 perfusion abnormality. However, the presence of a strongly positive exercise electrocardiogram only at heart rates of 140 beats/min or more or stage III or higher of the Bruce protocol was predictive of less extensive coronary disease and perfusion abnormalities.

Thus, the magnitude of ST depression as such during exercise is not predictive of the extent of coronary disease, even in patients with 3 mm or greater ST depression. However, a strongly positive exercise electrocardiogram in the first two stages of the Bruce protocol or at a heart rate of less than 140 beats/min was related to the extent of coronary artery disease and impaired myocardial perfusion, and identified patients with more extensive coronary artery disease and jeopardized myocardium. Therefore, caution should be used in interpreting prognostic data on the basis of the degree of exercise-induced ST depression alone.

Treadmill exercise testing has been used in the diagnosis of patients with coronary artery disease and in providing important prognostic information that may influence decisions regarding pharmacologic and surgical therapy. The prognosis of patients with coronary artery disease is determined primarily by the extent of the disease and the state of left ventricular function (1–3). The predictive value of treadmill exercise testing is directly related to the prevalence of the disease in the population studied (4,5). Several studies have addressed the value of treadmill exercise testing in identifying subsets of patients with coronary artery disease who are at high risk of cardiac complications and who may be candidates for elective diagnostic and therapeutic interventions (6–21). However, the relation among the severity of electrocardiographic abnormality during exercise, the extent and severity of coronary artery disease and left ventricular function has been controversial. The purpose of this study was to determine that relation in a fairly large number of patients.

Methods

Study patients. We reviewed our records and identified 229 consecutive patients who had undergone both treadmill exercise testing and coronary angiography within 6 months of one another. These patients were being evaluated for chest pain suspected of being angina pectoris. There were 177 men and 52 women, aged 30 to 75 years (mean 52). Patients with valvular disease and those who had undergone bypass surgery were excluded. One hundred seventy-one of these patients also had stress thallium-201 scintigraphy during treadmill testing.

Exercise electrocardiography. All patients were exercised in the fasting state in accordance with the standard Bruce protocol for treadmill exercise testing (22). Three electrocardiographic leads (V_3, V_5 and aVF) were monitored during exercise and recovery, and a 12 lead electrocardio-

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gram was obtained immediately after the termination of exercise. The end points for exercise were severe angina pectoris, with or without ST depression, excessive fatigue, leg weakness, dyspnea, hypotension or frequent premature ventricular complexes.

The exercise electrocardiograms were interpreted as positive, negative or inconclusive. A positive study was indicated by 1) 1 mm or greater horizontal or downsloping ST segment depression; 2) slowly rising ST segment with at least 1.5 mm depression 0.08 second after the J point; and 3) in the presence of ST segment depression at rest, an additional 2 mm of ST depression 0.08 second after the J point. The first type of abnormality was present in almost all of our patients with a positive exercise electrocardiogram. Horizontal or downsloping ST depression of 2.0 mm or greater was considered strongly positive. The exercise electrocardiogram was considered negative when the patient achieved at least 85% of the maximal predicted heart rate in the absence of ST segment changes. The exercise electrocardiogram was considered uninterpretable or inconclusive 1) when the patient failed to reach 85% of the predicted maximal heart rate in the absence of ischemic ST changes; 2) ST depression (0.5 mm or greater) appears in the electrocardiogram at rest without an additional 2 mm of ST segment depression during exercise; and 3) if bundle branch block, left ventricular hypertrophy or severe arrhythmia occurred during the test. Three patients, all of whom had positive exercise electrocardiograms during stage I or II of the Bruce protocol had exercise-induced hypotension. Two other patients had ventricular tachycardia during exercise, but their exercise electrocardiograms were uninterpretable. Few patients had ST segment depression only in the postexercise period; in these patients, the last stage of exercise was considered in the analysis.

The exercise electrocardiograms were evaluated by qualified independent observers without prior knowledge of the results of the other tests. Eight of the total 229 patients (6 with coronary artery disease and 2 normal subjects) had positive exercise electrocardiograms limited to lead aVF and were analyzed separately. The positive tests were further evaluated for maximal ST segment depression in lead V_5, the exercise stage during which maximal ST segment depression occurred and the exercise heart rate during which maximal ST segment depression occurred in lead V_5. In all minute more. Ten minutes after injection, images were obduring stress and recovery were recorded.

Thallium-201 imaging. At peak exercise, 2 mCi of thallium-201 was injected intravenously and flushed with dextrose and water. The patients continued to exercise for 1 minute more. Ten minutes after injection, images were obtained in the anterior, and the 30 and 60° left anterior oblique projections. Redistribution images were obtained 4 hours after exercise in the projections that showed perfusion abnormalities. The technique and interobserver and intraobserver variability in the interpretation of the scintigrams have been described in detail previously (22–25).

Finally, the size of the ischemic defects was quantitated by measuring the perimeter of the defect and expressing it as a percent of the total perimeter of the left ventricular image in that projection excluding the valve plane (23,26). The average size of the defect was obtained from the three projections.

Cardiac catheterization and angiography. Each patient underwent left and right heart catheterization, left ventriculography and coronary arteriography by standard techniques. Left ventriculography was performed in a 30° right anterior oblique projection (92 patients) or in biplane right and left anterior oblique projections (137 patients). Significant coronary artery disease was considered present if there was 50% or greater narrowing in the diameter of one or more of the major coronary arteries. In addition, we quantitated the extent of coronary artery disease, using a scoring system that takes into consideration the location and degree of narrowing in each of the major vessels and their branches (27). Each of the three major vessels was divided into three segments (proximal, middle and distal). If the degree of stenosis was less than 50%, a score of 0 was used; if 50 to 74%, a score of 1, if 75 to 99%, a score of 2; for total occlusion, a score of 3 was used. This score was multiplied by a factor that is dependent on the location of stenosis: a factor of 6 if in the left main coronary artery; a factor of 3 if proximal in each of the three major vessels; a factor of 2 if in the middle and a factor of 1 if distal. Finally, if the disease was in a diagonal branch of the left anterior descending artery or the marginal branch of the left circumflex artery, a factor of 1 was also assigned.

The left ventricular ejection fraction was measured from the contrast angiograms (28). Left ventricular wall motion was interpreted as normal or showing hypokinesia, akinesia or dyskinesia. The ejection fraction was derived from the following equation:

$$\text{Ejection fraction} = \frac{\text{End-diastolic volume} - \text{End-systolic volume}}{\text{End-diastolic volume}} \times 100.$$

The results of the cardiac catheterization were reviewed without knowledge of the other test results.

Statistical analysis. Statistical evaluation was performed using analysis of variance or the chi-square test when appropriate. A probability (p) value less than 0.05 was considered significant. Results are expressed as the mean ± standard deviation (SD) when applicable.

Results

Patients with coronary artery disease. A total of 179 patients had coronary artery disease: 148 men and 31 women (Table 1) with a mean age of 52 years (range 34 to 75).

Table 1. Patients (n = 179) With Coronary Artery Disease Classified According to the Results of Exercise Electrocardiograms

	Inconclusive Ex ECG		Positive Ex ECG		Negative Ex ECG		
	No (%)	Mean ± SD	No (%)	Mean ± SD	No (%)	Mean ± SD	p Value
Patients (no.)	77		79		23		
Age (yr)		54 ± 9		52 ± 8		48 ± 9	< 0.01
Men	58 (75)		72 (91)		18 (78)		NS
Women	19 (25)		7 (9)		5 (22)		NS
MI by ECG	23 (30)		12 (15)		3 (13)		NS
Propranolol therapy	54 (70)		37 (47)		6 (26)		< 0.001
Digitalis therapy	1 (1)		1 (1)		0 (0)		NS
Rest HR (beats/min)		66 ± 11		69 ± 14		74 ± 15	< 0.03
Rest SBP (mm Hg)		125 ± 18		128 ± 19		129 ± 17	NS
Rest DBP (mm Hg)		83 ± 11		85 ± 14		86 ± 10	NS
Ex HR (beats/min)		121 ± 23		136 ± 24		157 ± 25	< 0.0001
Ex SBP (mm Hg)		155 ± 24		155 ± 29		169 ± 30	< 0.01
Ex DBP (mm Hg)		89 ± 11		86 ± 12		93 ± 11	< 0.01
Ex rate-pressure product (beats/min·mm Hg)	$1.9 \times 10^4 \pm 5.3 \times 10^3$		$2.1 \times 10^4 \pm 6.7 \times 10^3$		$2.7 \times 10^4 \pm 6.5 \times 10^3$		< 0.001
Ex duration (min)		6.6 ± 3.4		7.0 ± 3.1		9.4 ± 2.7	< 0.01
Pts with Tl-201 studies	57 (74)		66 (84)		18 (78)		NS
Pts with abnormal Ex Tl-201 studies	46 (81)		57 (86)		13 (72)		NS
LVEDP (mm Hg)		18 ± 7		16 ± 6		15 ± 5	NS
LVEF (%)		59 ± 14		62 ± 12		67 ± 12	< 0.03
Wall motion							
Ak/dys	14 (18)		17 (22)		4 (17)		NS
Hypokinesia	44 (57)		40 (50)		10 (43)		
Normal	19 (25)		22 (28)		9 (39)		
CAD score		7.8 ± 4.7		9.1 ± 5.0		5.5 ± 3.8	< 0.006
Vessels with CAD							< 0.002
3	13 (17)		30 (38)		3 (13)		
2	28 (36)		22 (28)		5 (22)		
1	36 (47)		27 (34)		15 (65)		

*Statistical analysis performed by analysis of variance and chi-square testing. Ak/dys = akinesia/dyskinesia, CAD = coronary artery disease, DBP = diastolic blood pressure; ECG = electrocardiogram; Ex = exercise, HR = heart rate, LVEDP = left ventricular end-diastolic pressure, LVEF = left ventricular ejection fraction, MI = myocardial infarction, No. = number, NS = not significant, pts = patients, SBP = systolic blood pressure, SD = standard deviation; Tl-201 = thallium-201

Thirty-eight patients (21%) had electrocardiographic evidence (Q waves) of previous myocardial infarction. Of the 179 patients, 97 were receiving doses of a beta-receptor blocking agent (propranolol) and 2 were taking digitalis.

The exercise electrocardiograms were interpreted as positive in 79 patients (44%), negative in 23 (13%) and inconclusive in 77 (43%). The remaining 50 patients had normal coronary angiograms or insignificant (< 50% narrowing of one vessel) coronary artery disease.

Among the patients with coronary artery disease who had an interpretable exercise electrocardiogram, the sensitivity of the exercise electrocardiogram was 79% and that of exercise thallium-201 scintigraphy was 82%. Abnormal exercise thallium images were present in 81% of patients with coronary disease who had inconclusive exercise electrocardiograms. Among the patients with no coronary artery disease, the exercise electrocardiogram was negative in 25 (50%), positive in 12 (24%) and inconclusive in 13 (26%). Thus, the specificity of the test was 68% in patients with no coronary disease who had interpretable exercise electrocardiograms.

Magnitude of ST depression during exercise. The 179 patients with coronary artery disease were classified according to maximal ST depression during exercise (Table 2). There was no significant difference among the groups in exercise heart rate, blood pressure and exercise duration. Likewise, there was no difference in left ventricular end-diastolic pressure, number of diseased vessels, coronary artery score and presence and extent of exercise-induced perfusion abnormalities.

Among the 79 patients with coronary artery disease and a positive exercise electrocardiogram, the onset of ischemia was recorded in 67 patients. Thirty-one patients had early onset of ischemia (within 3 minutes) and 36 patients had ischemia after 3 minutes. There was no significant difference between these two groups in the incidence of one vessel disease (35 versus 39%), two vessel disease (39 versus 28%), three vessel disease (26 versus 33%) and coronary artery disease score (8.9 ± 4.7 versus 9.1 ± 4.8).

Patients with coronary artery disease and strongly positive exercise electrocardiograms. During exercise, 51 patients had 2 mm or greater ST depression in lead V_5.

Table 2. Patients With Coronary Artery Disease Classified According to Maximal ST Depression (ST^1)

	1–1.9 mm ST^1		2–2.9 mm ST^1		3 mm ST^1		
	No. (%)	Mean ± SD	No. (%)	Mean ± SD	No. (%)	Mean ± SD	p Value
Patients (no.)	28		24		27		
Age (yr)		50 ± 8		54 ± 6		52 ± 9	NS
Rest HR (beats/min)		73 ± 16		66 ± 12		68 ± 12	NS
Rest SBP (mm Hg)		128 ± 20		124 ± 20		132 ± 6	NS
Rest DBP (mm Hg)		86 ± 18		82 ± 13		87 ± 11	NS
Ex HR (beats/min)		134 ± 24		126 ± 20		148 ± 24	NS
Ex SBP (mm Hg)		160 ± 29		149 ± 26		155 ± 33	NS
Ex DBP (mm Hg)		87 ± 10		83 ± 10		87 ± 14	NS
Ex duration (min)		6 4 ± 2.3		6.8 ± 1 7		7 7 ± 3.4	NS
Pts with abnormal Ex Tl-201 studies	23 (96)		14 (78)		20 (83)		NS
% thallium abnormality		29 ± 15		27 ± 22		28 ± 17	NS
LVEDP (mm Hg)		16 ± 5		15 ± 7		18 ± 7	NS
LVEF (%)		61 ± 12		62 ± 9		63 ± 14	NS
Vessels with CAD							NS
1	10 (36)		11 (46)		9 (33)		
2	9 (32)		2 (8)		11 (41)		
3	9 (32)		11 (46)		7 (26)		
CAD score		8.8 ± 4.4		8 9 ± 5.4		9.5 ± 5 3	NS

Abbreviations as in Table 1

These patients were classified with respect to the exercise stage during which maximal ST depression appeared (Table 3). Maximal ST depression was present during stages I and II in 27 patients, and only during stage III or beyond in 24 patients. There was no significant difference in the magnitude of ST depression among these patients; however, the exercise heart rate and rate-pressure product (heart rate times systolic blood pressure) were higher in patients who exercised to stage III or beyond. Although the thallium scores showed less extensive defects in patients who demonstrated maximal ST depression only in stage III or above than in those who had ST depression in earlier stages, this difference was not statistically significant.

Left ventricular wall motion by contrast ventriculography was normal in 45% of patients with marked ST depression only in stage III or beyond, as compared with 15% of patients who had marked ST depression in earlier stages ($p < 0.05$).

The coronary artery disease score showed less extensive disease in patients who had marked ST depression only in stage III or beyond than in those with depression occurring at earlier stages, and three vessel disease was less frequent in patients with marked ST depression only in stage III or beyond than in those with depression occurring in the first two stages (25 versus 52%, $p < 0.05$).

Finally, the correlates of a strongly positive exercise electrocardiogram in relation to the exercise heart rate at which maximal ST segment depression appeared are shown in Table 4. More patients with a strongly positive exercise electrocardiogram at a heart rate of less than 140 beats/min were taking propranolol than were those who had a strongly positive exercise electrocardiogram at a higher heart rate. However, the variables—thallium score coronary artery disease score and presence of multivessel disease—were not different. Three vessel disease was more frequent in patients who had ST depression at a heart rate of less than 140 beats/min ($p < 0.05$). There was a greater prevalence of normal wall motion in patients with higher heart rates (12 versus 46%) ($p < 0.02$).

Exercise ST depression limited to lead aVF. Of the total population of 229 patients, only 8 had ST depression limited to lead aVF during exercise. Six of the eight had coronary artery disease (four with two vessel disease and two with one vessel disease) and two patients had normal coronary angiograms. Three percent of patients with coronary artery disease and 1% of normal subjects had ST depression limited to lead aVF.

False negative exercise electrocardiograms. Of 179 patients, 23 (13%) with coronary artery disease had a negative exercise electrocardiogram. These patients were compared with 79 patients (44%) who had a true positive exercise electrocardiogram. The incidence of previous myocardial infarction (as judged by Q waves) was similar in the two groups (15 versus 13%). Patients with a false negative exercise electrocardiogram achieved a higher heart rate (157 ± 25 versus 136 ± 24 beats/min, $p < 0.05$) and blood pressure (169 ± 30 versus 155 ± 29 mm Hg, $p < 0.05$) during exercise and had a longer exercise duration (9.4 ± 2.7 versus 7.0 ± 3.1 minutes, $p < 0.05$) than did patients with a positive exercise electrocardiogram. Propranolol therapy was more frequent in patients with a positive exercise electrocardiogram (47 versus 26%, $p < 0.05$). In

Table 3. Data in 53 Patients With Known Coronary Artery Disease and Strongly Positive Exercise Electrocardiogram

	Stages I to II Exercise ECG		Stage III or greater Exercise ECG		
	No. (%)	Mean ± SD	No (%)	Mean ± SD	p Value
Patients	27		24		
Age (yr)		55 ± 8		51 ± 7	NS
Men	23 (85)		23 (96)		NS
Women	4 (15)		1 (4)		NS
Propranolol therapy	12 (44)		7 (29)		NS
MI by ECG (Q waves)	5 (19)		2 (8)		NS
Ex HR (beats/min)		130 ± 26		147 ± 20	< 0 02
Ex SBP (mm Hg)		146 ± 29		160 ± 29	NS
Ex DBP (mm Hg)		84 ± 10		86 ± 15	NS
Maximal ST depression (mm)		3.0 ± 0 9		3.1 ± 0 9	NS
Ex rate-pressure product (beats/min·mm Hg)	$1\ 9 \times 10^4 \pm 7\ 2 \times 10^3$		$2.4 \times 10^4 \pm 5.9 \times 10^3$		< 0.02
Pts with abnormal Ex Tl-201 studies	19 (86)		15 (75)		NS
% thallium abnormality		32 ± 20		23 ± 17	NS
LVEF (%)		63 ± 10		63 ± 14	NS
Wall motion					<0.05
Ak/dys	8 (30)		4 (17)		
Hypokinesia	15 (56)		9 (38)		
Normal	4 (15)		11 (45)		
CAD score		10 9 ± 5 9		7 3 ± 3.9	< 0 02
Vessels with CAD					< 0.05
1	6 (22)		12 (50)		
2	7 (28)		6 (25)		
3	14 (52)		6 (25)		

Max = maximal, other abbreviations as in Table 1

addition, patients with a false negative electrocardiogram had lower coronary artery disease scores (5.5 ± 3.8 versus 9.1 ± 5.0, $p < 0.05$); only 35% of those patients had multivessel disease, compared with 66% of patients with a positive exercise electrocardiogram. The extent of wall motion abnormalities was similar in both groups.

In the patients who underwent stress thallium imaging, normal myocardial perfusion (false negative thallium scintigram) was twice as common in those with a false negative exercise electrocardiogram as in patients with a positive exercise electrocardiogram (28 versus 14%).

Inconclusive exercise electrocardiograms. Patients with coronary artery disease and an inconclusive exercise electrocardiogram were compared with patients who had a positive electrocardiogram. More women than men had an inconclusive exercise electrocardiogram (25 versus 9%, $p < 0.01$). A majority of these patients were taking a beta-blocking agent (70%).

Patients with an inconclusive exercise electrocardiogram had a lower exercise heart rate (121 ± 23 versus 136 ± 24 beats/min, $p < 0.05$) than patients with a positive exercise electrocardiogram. The coronary artery disease score (7.8 ± 4.7 versus 9.1 ± 5.0, $p < 0.05$) and prevalence of three vessel coronary artery disease (17 versus 38%, $p < 0.01$) were lower in patients with an inconclusive than in those with a positive exercise electrocardiogram.

Among those patients who had concomitant stress thallium scintigraphy, the thallium perfusion score was lower than in patients with a true positive test (22 ± 17 versus 28 ± 18, $p < 0.05$).

Patients with previous myocardial infarction. Of the 179 patients, 38 (21%) with coronary artery disease had electrocardiographic evidence of previous transmural myocardial infarction defined by abnormal Q waves (anterior infarction in 14, inferior or posterior in 24). Among these 38 patients, the exercise electrocardiogram was positive in 12 (32%), inconclusive in 23 (61%) and false negative in 3 (8%). Nine of the 12 patients with a positive exercise electrocardiogram had multivessel coronary disease compared with 15 of the 23 patients with inconclusive results (p= not significant [NS]).

Discussion

This study demonstrates that among patients with symptomatic coronary artery disease, the magnitude of ST depression during treadmill exercise testing was not related to the severity or extent of coronary artery disease, left ventricular

Table 4. Data in 51 Patients With Coronary Artery Disease and Strongly Positive Exercise Electrocardiogram in Relation to Exercise Heart Rate

	Ex HR <140 beats/min		Ex HR ≥140 beats/min		
	No (%)	Mean ± Standard Deviation	No. (%)	Mean ± Standard Deviation	p Value
Patients	25		26		
Age (yr)		54 ± 8		52 ± 7	NS
Men	23 (92)		23 (88)		NS
Women	2 (8)		3 (12)		NS
Propranolol therapy	16 (64)		4 (15)		< 0 0001
Rest HR (beats/min)		64 ± 7		71 ± 14	< 0.02
Ex SBP (mm Hg)		137 ± 24		167 ± 27	< 0.0002
Ex rate-pressure product (beats/min·mm Hg)		$1.6 \times 10^4 \pm 3.3 \times 10^3$		$2.6 \times 10^4 \pm 5.5 \times 10^3$	< 0.0000
Ex duration (min)		5.9 ± 2.7		8.8 ± 3.7	< 0.002
Max ST depression (mm)		2.9 ± 1 1		3.2 ± 7.1	NS
Time max ST depression (min)		2.9 ± 2.6		7.8 ± 4.7	NS
Pts with abnormal Ex Tl-201 studies	16 (84)		18 (78)		NS
% thallium abnormality		31 ± 21		25 ± 17	NS
LVEDP (mm Hg)		16 ± 7		18 ± 7	NS
LVEF (%)		62 ± 11		63 ± 13	NS
Wall motion					< 0.02
Ak/dys	5 (20)		7 (27)		
Hypokinesia	17 (68)		7 (27)		
Normal	3 (12)		12 (46)		
CAD score		10 6 ± 5.9		7 8 ± 4 5	NS
Vessels with CAD					
1	8 (32)		10 (38)		NS
2	3 (12)		10 (38)		NS
3	14 (56)		6 (23)		< 0.05

Max = maximal; other abbreviations as in Table 1.

function at rest or myocardial perfusion during stress. However, the occurrence of 2 mm or greater ST segment depression during exercise stage I or II, or at a heart rate less than 140 beats/min identified patients with more extensive coronary artery disease, left ventricular dysfunction and abnormal exercise myocardial perfusion. Although exercise test variables other than ST segment depression have been correlated with coronary arteriography, analysis of ST segment response remains the standard method (29,30).

Magnitude and Time of Onset of Exercise-Induced ST Segment Depression

Magnitude of ST depression. The relation between the magnitude of ST segment depression during exercise testing and the extent and severity of coronary artery disease has been controversial (8,12,13,21,29,31). Several investigators (20,21) suggested that specific electrocardiographic patterns during treadmill exercise testing were predictive of severe obstructive coronary artery disease, particularly left main artery disease. Bartel et al. (6) studied 332 patients with coronary artery disease who had interpretable exercise electrocardiograms and found that patients with three vessel or left main coronary stenosis had more severe ST segment depression. Similarly, Sanmarco et al. (29) and Goldman et al. (12) showed that ST segment depression of 3 mm or greater during exercise testing was predictive of and specific for extensive coronary artery disease. More recently, Stone et al. (21) reported on 60 patients with left main coronary artery disease undergoing treadmill exercise testing and found a higher rate of marked ST segment depression in patients with left main artery disease with a dominant left system or in association with disease of a dominant right coronary artery.

In contrast to these studies, our data demonstrated that patients with coronary artery disease who manifest various degrees of ST segment depression have similar values for left ventricular end-diastolic pressure ejection fraction, extent of coronary artery disease and myocardial perfusion. In agreement with our findings, Martin and McConahay (31) studied 63 patients with coronary artery disease and compared the severity of maximal ST segment depression during or after treadmill exercise with arteriographic extent of coronary artery disease. They showed that the incidence of multivessel disease was similar in patients who manifested 1 and 2 mm ST depression. They also found no correlation

between the extent of exercise-induced ST depression and rest left ventricular end-diastolic pressure or ejection fraction.

Weiner et al. (30) observed that although there was a high incidence of 2 mm or greater ST segment depression during exercise in patients with left main coronary artery disease, the magnitude of ST depression alone did not differentiate patients with left main or three vessel disease from patients with one or two vessel disease. Stated differently, of the 156 patients with coronary artery disease and exercise ST depression greater than 2 mm, 40% had one or two vessel coronary artery disease, 39% had three vessel disease and only 21% had isolated left main coronary artery disease.

Several factors may contribute to the apparent discrepancy among various studies. These include: patient selection, the number of electrocardiographic leads used (V_5 versus 12 lead electrocardiogram), the definition of the severity of coronary artery disease (50 versus 75% stenosis), criteria for a positive exercise electrocardiogram, particularly in the presence of resting ST abnormality, and the use of additional exercise testing variables such as time of onset of ST depression and heart rate at which maximal ST depression occurred.

Time of onset of ST depression. When our patients with coronary artery disease and marked ST segment depression were characterized as to the time of maximal depression or heart rate achieved, several interesting results were obtained. Patients who manifested maximal ST segment depression after 6 minutes of treadmill exercise (stage III, or beyond, Bruce protocol) tended to have significantly less extensive coronary artery disease, mild or no ventricular asynergy and less jeopardized myocardium during stress thallium scintigraphy than patients who had maximal ST depression in stages I or II. Although other investigators (8,10,13,21) demonstrated that the earlier onset of ischemic changes during the initial stage of exercise was a valuable indicator of the severity of coronary lesions, our results did not support these findings.

We further characterized patients with coronary artery disease and marked ST segment depression as to the maximal heart rate achieved. Patients with 2 mm or greater ST depression who achieved a peak heart rate of 140 beats/min or more tended to have less extensive coronary artery disease, less severe left ventricular wall motion abnormalities and less jeopardized myocardium during stress thallium-201 imaging. Bartel et al. (6) found that patients with positive stress tests who achieved a maximal heart rate of only 130 beats/min or less had a higher incidence of left main artery stenosis than did patients with a positive stress test and higher exercise heart rate.

Other factors in interpretation of marked ST depression. When interpreting the significance of marked ST segment depression during exercise, the time of maximal depression and the heart rate achieved must be considered. In addition, other factors must also be taken into account:

1. Patients with coronary artery disease who are taking maintenance doses of a beta-blocking agent tend to have a blunted heart rate response to exercise. In fact, more patients with marked ST segment depression who achieved a heart rate less than 140 beats/min were taking propranolol than were patients achieving a higher heart rate. However, this does not invalidate our conclusions; when we analyzed our data and included only patients who manifested electrocardiographic evidence of myocardial ischemia, there was no difference in the number of patients taking a beta-blocking agent with regard to the magnitude of ST depression or the stage of treadmill exercise testing during which maximal ST depression occurred.
2. Only 1% of our total patient population was taking digitalis immediately before exercise testing. The effect of digitalis on the interpretation of electrocardiographic response to exercise has been controversial (6,32,33); however, none of our patients with ST segment depression were taking digitalis.
3. Patients with coronary artery disease may manifest "chronotropic incompetence" and are unable to achieve a higher heart rate. Such patients were found to have a higher incidence of severe coronary artery disease and myocardial dysfunction (34,35). The difference in heart rate response among our patients with coronary artery disease and marked ST depression and the relation to the extent of coronary artery disease and abnormal myocardial perfusion are in agreement with the findings of these investigators.

Positive exercise electrocardiogram limited to lead aVF. Although a wealth of knowledge has been accumulated regarding exercise electrocardiography, little information is available as to the value of exercise-induced ST segment depression limited to the inferior electrocardiographic leads. Mason et al. (36) studied 56 patients with coronary artery disease and positive exercise electrocardiograms. Ischemia was limited to leads II, III and aVF in 14% of the patients. The incidence of ST segment depression in each of the isolated inferior leads was smaller. Other investigators (37) found the incidence of ST depression limited to the inferior leads to be one-tenth that of the left lateral leads. In our patient population, six (8%) of the patients with coronary artery disease and positive exercise electrocardiograms had ST depression limited to lead aVF. In addition, two normal subjects had ST depression limited to this lead.

False Negative Exercise Electrocardiograms

Of the patients with coronary artery disease in this study, 13% had a false negative exercise electrocardiogram. The incidence of false negative exercise electrocardiograms has

been reported to be between 2 and 68% (21,38–40). This disparity is largely due to population selection, the exclusion of patients with uninterpretable or inconclusive exercise electrocardiograms and the definition of the severity of coronary artery stenosis. Patients with a false negative exercise electrocardiogram in our study had less extensive coronary artery disease than did patients with a true positive exercise electrocardiogram. There was no difference in the incidence of prior myocardial infarction as judged by Q waves or left ventricular asynergy among patients with a false negative or a true positive exercise electrocardiogram. Our findings do not confirm the results of Kramer et al. (38) who found a higher incidence of left ventricular asynergy in patients with a false negative than in those with a true positive exercise electrocardiogram. Other authors (38,39) found a relation between false negative results and left ventricular asynergy or myocardial infarction (38,39).

Role of previous myocardial infarction and scar. Borer et al. (41) and Bartel et al. (6) confirm our findings that the presence of previous myocardial infarction does not influence the frequency of positive exercise electrocardiograms. Similarly, Stone et al. (21) found that a false negative exercise electrocardiogram occurred in 2% of 60 patients with left main coronary artery disease, despite a 30% incidence rate of prior myocardial infarction with corresponding wall motion abnormality. The reasons for the discrepancies in various reports are unclear. The presence of myocardial scar defined by Q waves on the electrocardiogram or by left ventricular asynergy ventriculography at rest is assumed to contribute to false negative exercise electrocardiograms. However, myocardial scars at rest as defined by angiography may be reversibly ischemic and may actually contain viable myocardium (42–45), and the presence of myocardial scars at rest in one segment does not preclude the occurrence of ischemia during exercise in the remaining myocardium, especially in patients with multivessel disease. Studies are in progress in our laboratory to determine the relation between the presence of myocardial scar and ischemia, as defined by exercise thallium-201 scintigraphy in patients with false negative exercise electrocardiograms.

Possible limitations of study. Biplane ventriculograms were not available in all patients in this study. The use of a single plane ventriculogram may result in underestimation of the regional wall motion abnormality and under- or overestimation of global ejection fraction (46–48). However, very few patients had a previous transmural infarction and this limitation should not influence the relation between the degree of ST segment depression and the extent of coronary artery disease. This study was retrospective, and therefore the results may be different in a prospective study. Finally, the exercise testing and coronary arteriography were performed within 6 months of one another. Progression of coronary artery disease is possible, but there was no change in the clinical status of the patients between the two studies.

Clinical Implications

Podrid et al. (49) reported a good prognosis for a group of patients with a strongly positive exercise electrocardiogram; very few of their patients had cardiac catheterization. Our results may help to explain these findings, because the extent of coronary artery disease did not differ significantly among patients with a mildly positive and those with a strongly positive exercise electrocardiogram.

Our data also showed that the extent of exercise-induced perfusion abnormalities is not affected by degree of ST depression. None of our patients with ST depression had other recognizable causes of ST depression, such as digitalis therapy or hyperventilation. The lack of correlation between degree of ST depression and anatomic and physiologic severity of coronary artery disease suggests other factors, not yet well defined, that may affect ST depression. Our findings indicate that 1) the degree of exercise-induced ST depression should not be the sole determinant of severity of coronary artery disease especially in prognostic studies, and 2) the exercise work load (duration of exercise) and heart rate achieved must be taken into account in interpretation of the exercise electrocardiogram.

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