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Prevalence of and Variables Associated With Silent Myocardial Ischemia on Exercise Thallium-201 Stress Testing

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The prevalence of silent myocardial ischemia was prospectively assessed in a group of 103 consecutive patients (mean age 59 ± 10 years, 79% male) undergoing symptom-limited exercise thallium-201 scintigraphy. Variables that best correlated with the occurrence of painless ischemia by quantitative scintigraphic criteria were examined. Fifty-nine patients (57%) had no angina on exercise testing. A significantly greater percent of patients with silent ischemia than of patients with angina had a recent myocardial infarction (31% versus 7%, $p < 0.01$), had no prior angina (91% versus 64%, $p < 0.01$), had dyspnea as an exercise test end point (56% versus 35%, $p < 0.05$) and exhibited redistribution defects in the supply regions of the right and circumflex coronary arteries (50% versus 35%, $p < 0.05$). The group with exercise angina had more ST depression (64% versus 41%, $p < 0.05$) and more patients with four or more redistribution defects.

However, there was no difference between the two groups with respect to mean total thallium-201 perfusion score, number of redistribution defects per patient, multivessel thallium redistribution pattern or extent of angiographic coronary artery disease. There was also no difference between the silent ischemia and angina groups with respect to antianginal drug usage, prevalence of diabetes mellitus, exercise duration, peak exercise heart rate, peak work load, peak double (rate-pressure) product and percent of patients achieving ≥85% of maximal predicted heart rate for age.

Thus, in this study group, there was a rather high prevalence rate of silent ischemia (57%) by exercise thallium-201 criteria. Patients with silent ischemia and those with exercise angina had comparable 1) exercise tolerance and hemodynamics, 2) extent of angiographic coronary artery disease, and 3) extent of exercise-induced hypoperfusion. Finally, more patients with recent infarction had silent ischemia than had exercise angina.

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Recent studies (1,2) estimate that as many as 70% of ischemic episodes in patients with coronary artery disease are unassociated with angina. Despite the absence of pain, these ischemic episodes have been shown to have prognostic utility in the patient with unstable angina pectoris (3,4) or recent myocardial infarction (5) and are important in defining the total ischemic burden in the patient with known coronary artery disease.

Among the mechanisms believed to be important in determining which ischemic episodes are silent, investigators (6) have cited differences in pain threshold and tolerance, duration of ischemia, myocardial denervation and predisposing disease states. Conflicting data (7) have been reported regarding the influence of the extent of ischemia on the development of ischemic pain. Both the mechanisms and the prognostic significance of silent ischemia are thought to vary in different clinical subgroups.

Many studies of silent ischemia have examined the painless ischemic response by analyzing ST depression during graded exercise testing or ambulatory Holter electrocardiographic (ECG) monitoring in patients with known anatomic evidence of disease. Although in many patients transient ST segment depression represents myocardial ischemia, false positive ST depression, particularly in the asymptomatic (8) and postinfarction (5) patient, confounds analysis and hence the prognostic value of the ECG response.

Thallium-201 imaging may yield important supplementary information in assessing patients with possible silent ische-

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mia (9). Perfusion imaging with thallium-201 is more sensitive and specific for the ischemic response than is ST depression analysis, can define the anatomic localization of ischemia and will detect ischemia in the presence of baseline ECG abnormalities. Enhanced sensitivity of thallium-201 scintigraphy compared with the ST segment response was reported by Esquivel et al. (10) at all levels of exercise. Additionally, the prognostic value of thallium-201 redistribution in patients with known coronary artery disease and in the asymptomatic postinfarction patient has been reported (11–13) to be superior to that of exercise ST depression alone.

By employing thallium-201 perfusion imaging, we sought to prospectively determine the prevalence of a silent ischemic response in a group of patients who underwent symptom-limited exercise thallium-201 testing. We tested the hypothesis that the occurrence of silent ischemia is independent of exercise performance variables such as achieved heart rate or work load. Finally, we sought to identify those clinical, exercise test and angiographic variables that best correlated with the occurrence of painless ischemia by exercise thallium-201 scintigraphic criteria.

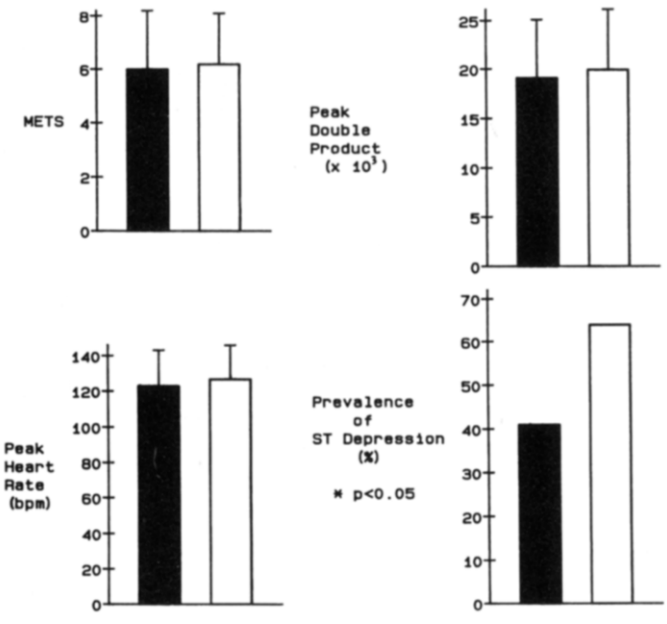


Figure 1. Comparison of silent ischemia (**solid bars**) and angina (**open bars**) groups with respect to exercise test variables.

Methods

Study patients. Patients were selected prospectively and consecutively from 605 patients who underwent exercise stress testing in conjunction with thallium-201 perfusion imaging at the University of Virginia Medical Center during the period October 20, 1987 through April 1, 1988. During this period, 327 patients had an abnormal scan; of these, 140 had solely persistent defects with no evidence of redistribution. The remaining scans were examined by two investigators (G.B. and C.G.) who had no prior knowledge of ECG or angiographic results. Only consecutive patients who had unequivocal evidence of thallium-201 redistribution by quantitative criteria and who underwent symptom-limited exercise testing were included. Patients undergoing submaximal exercise testing who did not achieve symptom-limited end points were not included.

One hundred three patients fulfilled study entry criteria. Seventy-four (72%) were referred for stress testing for evaluation of chest pain. Twenty-one patients (20%) were tested after a recent infarction experienced within 10 days of exercise testing and 41 patients (40%) had had a remote infarction defined as history of infarction >6 weeks before exercise testing. Twenty (19%) of the 103 patients had baseline ST segment abnormalities at rest.

Graded exercise testing. All 103 patients underwent symptom-limited exercise treadmill testing according to the Bruce (n = 82) or the Naughton (n = 21) protocol. Medications were not withdrawn before testing. Baseline heart rate, ECG and blood pressure were recorded at rest, at each minute of exercise and at 1, 2, 3, 4 and 5 min after exercise or until resolution of symptoms. Time of onset and resolution of ST segment depression and symptoms was also recorded. Exercise end points included exercise-limiting chest pain, dyspnea (breathlessness), fatigue, lower limb claudication, a decrease in blood pressure ≥10 mm Hg below the peak value at the previous stage, >2 mm ST segment depression and ventricular tachycardia (>15 consecutive beats). History of chest pain and character of limiting chest pain during exercise were designated as typical or atypical angina by the examining physician for each patient.

Exercise tests were read by two independent readers and considered abnormal if ≥1 mm ST depression 80 ms beyond the J point was noted in three consecutive beats of a flat baseline. The ECG responses in the presence of preexisting left bundle branch block, digitalis therapy and left ventricular hypertrophy were considered nondiagnostic, as was a normal ECG response in patients who did not achieve ≥85% of maximal predicted heart rate.

Thallium-201 imaging. For all patients, a dose of 1.5 to 2.0 mCi of thallium-201 chloride was administered intravenously at peak exercise. Exercise was continued for 60 to 90 s longer after thallium-201 injection. Initial (10 min after exercise) and delayed (after 2 h) images were acquired in the anterior and 45° and 70° left anterior oblique projections. Quantitative analysis of seven myocardial segments (Fig. 1) was performed with a computer-based method and analyzed by two independent observers unaware of other patient data, as previously described (14). Redistribution was considered present if the ratio of activity in an abnormal segment increased in the delayed images compared with the initial

images. A segment was considered abnormal if it had ≤25% activity compared with the initial segment in the same view with the greatest activity. In this study, isolated abnormal washout from a segment was also considered to be a redistribution defect.

Cardiac catheterization. Eighty-three patients underwent coronary angiography by decision of the attending physician. Only 71 of these coronary angiograms performed within 1 year of exercise stress testing were analyzed. The only significant difference between the 71 patients who underwent angiography and the total study group was the higher prevalence of diabetes in those who underwent cardiac catheterization. However, only 24 of the entire cohort of 103 patients had diabetes. There was no difference between the angiography group and the total study cohort with respect to percent of patients with angina during exercise testing, extent of thallium-201 perfusion abnormalities, exercise tolerance and prevalence of exercise-induced ST depression.

Severity of stenotic lesions was assessed by visual analysis with use of a hand-held caliper. Stenoses were graded as ≥50% and classified by the projection showing the most significant stenosis. Each patient was recorded as having one, two or three vessel disease. Involvement of the proximal coronary arteries was also noted. Any differences in interpretation encountered in two separate blinded readings of each study were reconciled by a consensus interpretation (L.B. and C.G.). Left ventricular end-diastolic pressure was recorded and left ventricular ejection fraction was determined by ventriculographic methods. A jeopardy score as described by Dash et al. (15) was derived.

Data analysis. Data analysis was performed with Student's *t* test for continuous data and either the Fisher exact test or the chi-square test for noncontinuous data. Results are expressed as mean value ± 1 SD or as a percent. The statistical power to detect a difference in the variables analyzed between the silent ischemia and angina groups was conditioned on some differences actually existing. In most instances, the probability of detecting a difference was 90%.

Results

Patient characteristics (Table 1). The mean age of the 103 patients in this study was 59 ± 10 years. Eighty-one patients (79%) were male and 78 (76%) had a history of prior angina. Forty-one patients (40%) had an infarction >6 weeks before testing and 21 (20%) had a recent infarction within 10 days of testing. Ten percent of patients underwent coronary bypass surgery ≤10 years before testing. Twenty-four patients (23%) had a history of diabetes mellitus; of these, six required insulin.

Of the 103 patients studied, 59 (57%) had no angina during exercise testing (Group I) and were considered to have exercise-induced silent ischemia. The remaining 44 patients (43%) had angina pectoris during the exercise test (Group II). The silent ischemia and angina groups are compared with respect to clinical variables in Table 1. A significantly greater percent of Group I compared with Group II patients had recent infarction (31% versus 7%, $p < 0.01$). Group II patients were more likely to have a history of prior angina than were Group I patients (91% versus 64%, $p < 0.01$).

Table 1. Comparison of Silent Ischemia and Angina Groups With Respect to Clinical Variables

Variables	Silent Ischemia (n = 59)	Angina (n = 44)	p Value
Age (yr)	59 ± 11	59 ± 10	NS
Male gender (%)	78	79	NS
Prior infarction (%)			
Remote	44	34	NS
Recent	31	7	<0.01
Prior angina (%)	64	91	<0.01
Diabetes mellitus (%)	24	23	NS
Beta-adrenergic blockers (%)	22	39	NS
Nitrates (%)	49	41	NS
Calcium antagonists (%)	63	52	NS

Graded exercise testing (Table 2, Fig. 1). For the entire cohort, there was no difference between the two groups with respect to use of antianginal medication at the time of exercise testing, exercise duration (regardless of protocol), peak exercise systolic blood pressure or percent of patients achieving maximal predicted heart rate for age. There was no difference between the two groups with respect to work load achieved, peak exercise heart rate or peak double (rate-pressure) product (Fig. 1). Fifty-nine percent of patients in Group II (angina) versus 39% of patients in Group I (no angina) had ≥1 mm ST depression ($p < 0.05$).

There was no difference between the two groups with respect to frequency of ST depression on the baseline ECG, digoxin therapy preexisting left bundle branch block, time of onset or duration of ST depression, percent of patients with exercise hypotension (defined as a decrease in blood pres-

Table 2. Comparison of Silent Ischemia and Angina Groups With Respect to Exercise Test Variables

	Silent Ischemia (n = 59)	Angina (n = 44)	p Value
Peak systolic BP (mm Hg)	154 ± 34	158 ± 28	NS
<85% MPHR (%)	68	53	NS
Exercise duration (min)			
Bruce protocol	5 ± 2	5 ± 2	NS
Naughton protocol	11 ± 5	8 ± 4	NS
Exercise hypotension (%)	24	25	NS
Exercise arrhythmias (%)	19	14	NS
Exercise dyspnea (%)	56	36	<0.05
ST depression ≥1 mm (%)	41	64	<0.05
Duration of ST depression (min)	5 ± 4	7 ± 3	NS

BP = blood pressure; MPHR = maximal predicted heart rate for age.

Table 3. Comparison of Silent Ischemia and Angina Groups With Respect to Thallium-201 Scintigraphic Variables

	Silent Ischemia (n = 59)	Angina (n = 44)	p Value
Total perfusion score	16.7 ± 4.8	15.7 ± 4.8	NS
No. redistribution defects/pt.	2.3 ± 1.2	2.5 ± 1.4	NS
↑ lung uptake (%)	24	32	NS
Persistent defects (%)	29	21	NS
LAD redistribution (%)	49	60	NS
RCA/LCx redistribution (%)	50	35	<0.05
Indeterminate redistribution (%)	1	5	NS
Multivessel redistribution (%)	25	25	NS

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; pt. = patient; RCA = right coronary artery; ↑ = increased.

sure of ≥10 mm Hg at peak exercise) or prevalence of exercise-induced arrhythmias (frequent premature ventricular complexes, multiform premature ventricular complexes or ventricular tachycardia). Symptoms present in Group I patients that limited exercise were dyspnea (n = 32), fatigue (n = 21), claudication (n = 3), ventricular tachycardia (n = 1), dizziness (n = 1) and marked ST depression (n = 1). A greater percent of Group I compared with Group II patients reported dyspnea during the exercise test (56% versus 36%, $p < 0.05$).

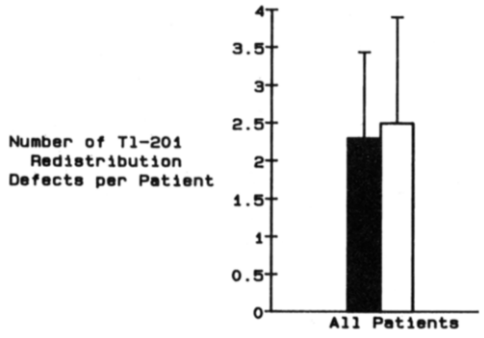
Thallium-201 scintigraphic variables (Tables 3 and 4). There was no significant difference between the two groups with respect to total thallium-201 perfusion score, percent of patients with abnormal thallium-201 lung uptake, percent of patients with multivessel thallium-201 redistribution, apical redistribution or redistribution in the supply region of the left anterior descending coronary artery. Patients in Group I (silent ischemia) had a greater percent of redistribution defects in the supply regions of the right coronary and left circumflex arteries.

To compare the extent of redistribution between the two groups, the number of redistribution segments was summed for each patient and the ratio of redistribution defects to total defects (expressed as a percent) derived. The latter was used as an index of the extent of ischemia relative to the total extent of hypoperfusion, which could include areas of prior infarction. There was no significant difference between Groups I and II with respect to the number of redistribution defects per patient (2.3 ± 1.15 versus 2.5 ± 1.39, respectively). Group II patients tended to have more redistribution defects as a percent of total defects per patient, but this difference was not statistically significant (0.81 versus 0.74, respectively, $p = 0.1$) (Fig. 2). When we compared the two groups with respect to patients with more extensive ische-

Table 4. Subgroup of Patients With Both Ischemic ST Depression and Thallium-201 Redistribution

No. of Patients (%)	Exercise-Induced Silent Ischemia (n = 23; 39%)	Exercise-Induced Angina (n = 26; 59%)	p Value
Tl-201 variables			
Tl-201 perfusion score	16.9 ± 4.8	15.5 ± 3.9	NS
No. with lung uptake	6	7	NS
No. redistribution segments/pt	2.2 ± 1.1	2.7 ± 1.3	=0.06
Ratio of redistribution (defects/total defects)	0.74	0.84	=0.09
Exercise variables			
METs achieved	6.9 ± 2.6	6.7 ± 1.6	NS
Peak heart rate (beats/min)	126.0 ± 12.3	130.0 ± 19.1	NS
Peak rate-pressure product	19.2 ± 5.9	20.9 ± 6.3	NS
Peak systolic blood pressure (mm Hg)	150.0 ± 4.0	161.4 ± 28.0	NS
ST variables			
Time at onset of ST depression (min)	3.81 ± 0.3	3.59 ± 0.3	NS
METs at onset of ST depression	5.2 ± 2.0	5.3 ± 1.5	NS
Heart rate at onset of ST depression (beats/min)	117.7 ± 17	117.9 ± 17	NS
Systolic blood pressure at onset of ST depression (mm Hg)	140.0 ± 33.0	152.0 ± 21	NS
Duration of ST depression (min)	5.3 ± 3.6	6.2 ± 3.2	NS
Patients with history of myocardial infarction (all) (no. of patients)	15 (65%)	10 (38%)	<0.05
Remote infarction	13 (56%)	9 (35%)	=0.16
Recent infarction	2 (9%)	1 (4%)	NS
Medication use (no. of patients)			
Calcium channel blockers	13 (57%)	16 (62%)	NS
Beta-adrenergic blockers	9 (39%)	11 (42%)	NS
Nitrates	11 (48%)	10 (38%)	NS

METs = metabolic equivalents; Tl-201 = thallium-201.



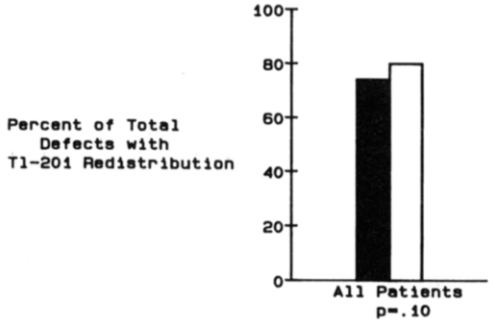
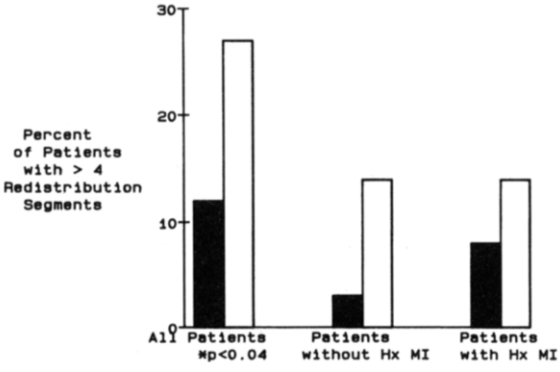


Figure 2. Comparison of silent ischemia (**solid bars**) and angina (**open bars**) groups with respect to extent of t' allium-201 (Tl-201) redistribution.

mia, more patients in Group II had four or more redistribution segments (Fig. 3).

Influence of prior infarction. We assessed whether a history of remote or recent myocardial infarction influenced which patients were more likely to have silent ischemia by thallium-201 scintigraphic criteria (Fig. 4). There was no difference between Group I and Group II with respect to the frequency of patients with a history of remote infarction.

Figure 3. Prevalence of extensive (four or more segments) thallium-201 redistribution in silent ischemia (**solid bars**) and angina (**open bars**) groups. Hx MI = history of myocardial infarction.



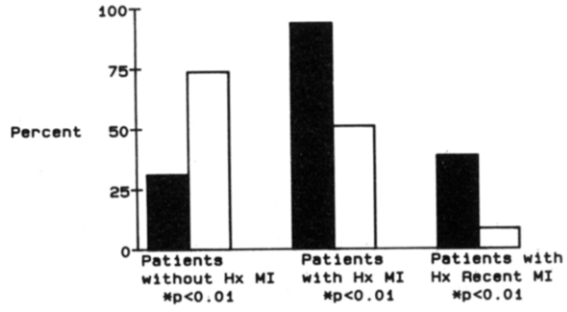


Figure 4. Percent of patients with silent ischemia (**solid bars**) and angina (**open bars**) without a history (Hx) of myocardial infarction (MI), with a history of myocardial infarction and with a history of recent (<6 weeks) myocardial infarction.

More patients in Group I had a history of recent infarction (31% versus 7%, $p < 0.01$).

Coronary angiography (Table 5). There was no difference between Group I and Group II with respect to baseline ejection fraction (55 ± 13% versus 54 ± 14%) or jeopardy score (7.3 ± 3.7 versus 7.5 ± 3.5). There was no difference between groups with respect to the frequency of one, two or three vessel disease and the occurrence of any significant disease in one specific vessel, whether the left anterior descending, left circumflex or right coronary artery. Frequency of significant stenosis in the proximal left anterior descending artery did not differ between groups, nor did the number of patients with significant stenosis in one, two or three proximal vessels. Of the patients with proximal vessel disease, those who exhibited silent ischemia were no more likely than patients with exercise-induced angina to have multivessel proximal disease rather than disease in one proximal vessel.

Patients with both ST depression and thallium-201 redistribution (Table 4). Forty-nine patients had both quantitative redistribution by thallium-201 criteria and ischemic ST depression. Of these, 23 patients (47%) had silent ischemia and 26 (53%) had angina pectoris. Within this subgroup, those with silent ischemia or angina had similar times of

Table 5. Comparison of Silent Ischemia and Angina Groups With Respect to Angiographic Variables

Variable	Silent Ischemia (n 43)	Angina (n = 28)	p Value
Single vessel disease (%)	30	21	NS
Multivessel disease (%)	70	79	NS
LVEF (mean ± SD)	55 ± 13	54 ± 14	NS
Jeopardy score	7.3 ± 3.7	7.5 ± 3.5	NS
LAD disease (%)	49	41	NS
LCx disease (%)	36	34	NS
RCA disease (%)	34	32	NS

≥50% stenosis considered significant. LVEF = left ventricular ejection fraction; other abbreviations as in Table 3.

onset and duration of ST depression. Also, there was no difference in heart rate, metabolic equivalents (METs) achieved and systolic blood pressure at the onset of ST depression. At peak exercise, patients with silent ischemia or angina were similar with respect to extent of hypoperfusion and extent of ischemia. Angiographic jeopardy score was similar in these patients, as was presence of multivessel disease.

Discussion

Our study attempted to determine the prevalence of painless ischemia as defined by thallium-201 scintigraphy during exercise testing in patients with coronary artery disease and to identify which variables play a role in influencing whether angina does or does not occur. Our study differs from other studies of exercise-induced silent ischemia in that 1) we employed thallium-201 redistribution by quantitative criteria as the marker of ischemia in conjunction with symptom-limited exercise testing in a group of prospectively studied consecutive patients referred for exercise stress testing, and 2) an abnormal ECG response to exercise testing was not, in itself, a criterion for inclusion. By employing this scintigraphic definition of silent ischemia, we were able to include patients with perfusion abnormalities consistent with ischemia who might have been excluded in other studies because of either baseline ECG abnormalities or a normal exercise ST segment response.

The main findings of our study were 1) silent ischemia (absence of angina) is quite prevalent during exercise thallium-201 stress testing; 2) there was no significant difference in extent of exercise-induced ischemia between patients who had silent ischemia and those who manifested exercise angina; and 3) patients with silent ischemia and patients with angina had comparable exercise tolerance and a similar extent of angiographic coronary artery disease.

Prevalence of silent ischemia. In this prospective study, we found a rather high prevalence rate of silent ischemia (57%) when thallium-201 redistribution was utilized to define a positive ischemic response during exercise testing. This prevalence is (slightly) higher than that reported by other investigators (16–18), perhaps because we included patients with recent myocardial infarction, who are known to exhibit a high incidence of asymptomatic ischemia during exercise testing. Our patient cohort was also representative of the heterogeneous group of patients with coronary artery disease referred for exercise testing. Although all our patients exhibited ischemia by thallium-201 quantitative criteria, 54 patients (52%) included in our study would have been excluded if ST segment criteria for ischemia alone had been utilized for study inclusion. Of these 54, 20 of the study group (19%) had baseline ECG abnormalities (that is, left ventricular hypertrophy, digoxin therapy, left bundle branch block) that would yield a noninterpretable ECG response. These patients with baseline ECG abnormalities did not differ from the total sample in the frequency of silent ischemia or angina. The remaining 34 patients (33%) had no ECG abnormalities at rest but had exercise-induced thallium-201 redistribution with no ST depression.

"Silent" thallium-201 redistribution defects. The significance of painless thallium-201 redistribution abnormalities in patients undergoing exercise testing has not been extensively evaluated. Reisman et al. (19) employed thallium-201 imaging to study a large group of patients with no prior history of infarction or bypass surgery. From this group, they identified a subset of patients who, although without angina during treadmill testing, manifested decreased exercise tolerance and thallium-201 redistribution defects. This subset of patients with redistribution defects was at high risk for future cardiac events. In a retrospective analysis of 55 patients with angiographically documented coronary artery disease, Assey et al. (20) found a higher incidence of subsequent acute myocardial infarction at 30 month follow-up evaluation in patients with reversible thallium-201 defects and no angina compared with patients with reversible thallium-201 defects associated with angina. Other groups have reported a substantially higher prevalence of thallium-201 redistribution than anginal-type chest pain during exercise testing (14,21). In one of these studies (14), multivariate analysis revealed that the presence of angina during exercise testing did not have independent predictive value for identifying high risk patients beyond that of thallium-201 and ST segment variables alone.

The clinical implication of our findings and those of previous studies is that prognosis is likely more related to extent and severity of ischemia independent of whether or not chest pain is induced on a particular exercise stress test. In the present study, many patients with silent ischemia had multiple thallium-201 defects in several coronary supply regions.

Clinical variables. The clinical variables identified in our patients as being significantly associated with the presence of silent exercise-induced ischemia are similar to those reported in previous studies (22–24). We found that patients with a history of prior angina were more likely to experience exercise-induced angina, confirming the observations of Mark et al. (24). Patients with a history of myocardial infarction, particularly recent infarction, are more likely to experience exercise-induced silent ischemia (22). Our findings are similar in this regard. We found no difference between groups with respect to age, gender, medication usage or incidence of diabetes mellitus.

Exercise test variables. Patients with exercise-induced silent ischemia and those with exercise-induced angina during exercise testing were not different with respect to exercise duration or exercise peak heart rate, peak work load, peak systolic blood pressure, percent of patients achieving ≥85% of maximal predicted heart rate for age or peak double

(rate-pressure) product achieved. This is in contrast to previous studies (21–23) that reported a higher work load and heart rate in patients with silent ischemia compared with those with angina during exercise testing. Three factors might account for patients with silent ischemia achieving a higher work load as reported in the studies cited compared with comparable exercise end points achieved in our study: 1) One must consider the possibility of false positive ST depression when using ≥1 mm ST depression as a criterion for inclusion; that is, certain patients may have been included in previous studies who achieved a high exercise heart rate and exhibited a false positive ST response and, thus, were misclassified as having silent ischemia. 2) Because significant ST depression has been noted to occur at higher heart rates (25) than do thallium-201 defects, the selection of patients based solely on the presence or absence of ST depression also selects patients with a higher heart rate and higher rate-pressure product in the ST depression group. This biased selection confounds the variables being analyzed and limits conclusions regarding exercise performance variables in studies that utilize ST depression as the sole criterion for inclusion. 3) It is possible that among patients with significant exercise-induced ST depression, those who develop angina may stop exercising at an earlier exercise time because of the very presence of angina itself, thereby limiting their performance.

Presence of ST depression. Our selection of patients with silent ischemia based on quantitative thallium-201 redistribution permitted the analysis of the significance of concomitant ischemic ST depression. For the entire group of 103 patients, a significantly higher percent of patients in Group II with exercise-induced angina had both thallium-201 redistribution and ST depression compared with those patients with silent ischemia in Group I (64% versus 41%). In a prognostic study of exercise-induced ischemia in a group of 131 mildly or asymptomatic patients, Bonow et al. (26) studied the significance of concomitant ST depression in patients with ischemia as demonstrated by exercise radionuclide angiography. They found that patients who developed angina during exercise testing were more likely to exhibit a positive ST segment response (71%) than patients with silent ST depression (53%). When Bonow et al. (26) examined the ischemic response with respect to angiographic extent of coronary artery disease, they found a greater prevalence of left main coronary and three vessel disease in patients who developed angina during exercise testing. Their study (26) differs from ours in that we studied principally symptomatic patients and found a similar extent of coronary artery disease between patients who did and did not develop angina during exercise testing (see below).

For the subgroup of patients with both exercise-induced thallium-201 redistribution and ischemic ST depression, the time of onset and work load at onset of ST depression did not differ from values for patients with exercise-induced angina and ischemic ST depression. In a recent study of silent ischemia detected during ambulatory monitoring, Mulcahy et al. (27) found that the change in heart rate from baseline to the ischemic ECG response during exercise testing was no different for patients who demonstrated either silent or painful ischemia on ambulatory ECG monitoring, implying a similar pathophysiology for ischemia associated with angina to that which is silent. Mulcahy et al. (27) did note, however, that ischemic ST depression (both silent and associated with angina) occurred at a lower heart rate during ambulatory monitoring than at the onset of ST depression during exercise testing. Their study provided no information that correlated the presence or absence of silent ischemia during ambulatory monitoring in patients whose ECG response during exercise testing indicated silent ischemia.

Extent of perfusion abnormalities. We examined whether differences existed in the extent or severity of perfusion abnormalities between the silent ischemia and angina groups. Another recent study (18) employed myocardial perfusion imaging to study the amount of myocardium in jeopardy in patients with silent ischemia. In that study of 113 consecutive patients referred for cardiac catheterization, Hecht et al. (18), using quantitative single photon emission computed tomographic thallium-201 imaging, found no difference in the number of redistribution defects per patient between those with silent ischemia and those with exercise angina. Similarly, in the present study, we found no difference between the two groups with respect to the number of redistribution defects per patient, although there was a trend toward more extensive redistribution in patients with exercise-induced angina than in patients with exercise-induced silent ischemia. Patients with more extensive ischemia, defined as exhibiting four or more redistribution segments, were significantly more likely to have angina during exercise testing than those with less extensive ischemia.

Extent of angiographic disease. When we examined the ischemic response in relation to angiographic extent of coronary artery disease, we found no difference in the percent of patients with one, two or three vessel disease by angiography or in baseline left ventricular ejection fraction between the silent ischemia and angina groups (22,23,28). The Coronary Artery Surgery Study (CASS) (23) and a recent study by Mark et al. (24) did report a higher incidence of three vessel disease in patients with angina than in patients with silent ischemia as defined by ST depression criteria. Bonow et al. (26), as noted previously, also reported a higher prevalence of left main and three vessel disease in their study cohort. Importantly, our patients, who included both inpatients and out of hospital patients, may be different from those described in these other studies, particularly the selection of patients with ischemia and the selection of patients for angiography.

Significance of prior infarction. We found that patients with a history of myocardial infarction were more likely to

exhibit silent ischemia than angina during exercise testing. We used a ratio of redistribution defects to total number of initial defects as an index of the extent of ischemia. There was no difference in this index of extent of ischemia between patients in Groups I and II who had a history of prior infarction. Thus, patients with silent ischemia or angina and prior infarction had a comparable extent of exercise-induced ischemia. Stern et al. (28) also found that postinfarction patients had a slightly greater prevalence of silent ischemia on ambulatory monitoring (75%) than did patients without a history of infarction (65%).

Our subgroup of patients with recent infarction had a particularly high incidence of silent ischemia. Ouyang et al. (16) also reported a high incidence (63%) of silent ischemia (although by ECG criteria) among recent postinfarction patients with a positive exercise test response independent of exercise rate-pressure product, heart rate, exercise duration or extent of angiographic coronary artery disease. Ouyang et al. (16) also found a higher incidence of inferior myocardial infarction in patients with silent ischemia.

As do patients who have undergone transplantation or coronary bypass surgery (29), patients with recent infarction may undergo a phase of denervation that increases their threshold to pain, a process that may differ with extent or location of infarction.

Gibson et al. (21) reported a higher incidence of right coronary or left circumflex infarction in patients with recent infarction who demonstrated painless ST depression during submaximal exercise testing. In our study, we found a higher prevalence of right coronary artery and left circumflex artery redistribution abnormalities in patients with silent ischemia (50%) than in patients with angina (35%) during exercise testing. The significance of this finding is uncertain at this time.

Study limitations. Our prospectively sampled consecutive series of patients were referred for exercise testing largely to evaluate a spectrum of angina. Many had had recent admissions to the hospital for rest episodes of angina and their condition had subsequently stabilized. Not all underwent coronary angiography. Medications were not withdrawn before testing. Our results might not reflect repeat testing for the same patient nor be properly generalized to other studies that use ambulatory ST depression analysis. This caveat is particularly important in considering that mechanisms of ischemia may differ in different subgroups and at different times.

Conclusions. Despite certain limitations, our findings indicate a high prevalence of silent ischemia as defined by thallium-201 scintigraphic criteria during exercise stress testing. The high prevalence of silent ischemia noted in this study has important clinical implications because a substantial number of patients with silent ischemia might not have been identified by ECG stress testing alone. Using a radionuclide criterion for ischemia, we were able to include patients who might not have been identified by ECG stress testing alone and excluded patients with potentially false positive ECG responses. The thallium-201 imaging data also permitted the assessment of the extent of exercise-induced hypoperfused myocardium, which cannot be achieved by analysis of ST segment data alone. We confirm previous reports of a high incidence of silent ischemia in postinfarction patients. We found that patients with silent ischemia and those with exercise angina had comparable exercise tolerance, a similar extent of angiographic coronary artery disease and a similar extent of exercise-induced hypoperfusion. Further studies are needed to evaluate treatment strategies based on identifying patients with silent ischemia in this manner and to correlate other forms of testing with the results obtained.

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