JACC Vol. 14, No. 4
October 1989:895–900

Silent Ischemia: Evaluation by Exercise and Redistribution Tomographic Thallium-201 Myocardial Imaging

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To compare the amount of myocardium jeopardized during silent ischemia and painful ischemia, 112 consecutive patients undergoing coronary arteriography with ischemia demonstrated by exercise and redistribution tomographic thallium-201 myocardial imaging (SPECT) were divided into two groups: 84 patients without anginal pain (silent ischemia) and 28 with pain (painful ischemia). The SPECT apical, mid and basal ventricular levels of the short-axis view and the apical portion of the long-axis view were divided into 20 segments.

The results were 1) 7.4 ± 4.7 ischemic segments in silent ischemia and 7.6 ± 3.7 in painful ischemia (p = NS) with 4.7 ± 3.6 segments in silent ischemia undergoing total redistribution compared with 5.4 ± 3.4 in painful ischemia (p = NS); 2) no difference in the incidence of single, double or triple vessel disease between silent and painful ischemic groups; 3) similar anatomic distribution of ischemic segments between the two groups; 4) more positive exercise electrocardiographic (ECG) changes in painful ischemia (70%) than in silent ischemia (32%) ($p < 0.001$) with equal amounts of ischemia associated with positive and negative exercise ECG findings.

Conclusions: 1) Patients with silent and painful ischemia during exercise have similar amounts of ischemic myocardium demonstrated by tomographic thallium-201 imaging and similar extent of angiographically documented coronary artery disease despite the absence of pain and the lower incidence of positive exercise ECG findings in silent ischemia. 2) Positive and negative exercise ECG findings were associated with similar amounts of ischemic myocardium.

(J Am Coll Cardiol 1989;14:895–900)

Whereas many reports have documented a similar degree of coronary artery disease (1–7) and a similar (1–6,8,9) or worse (7) prognosis in patients with silent ischemia compared with patients experiencing angina with exertion, there is a paucity of data (10,11) comparing the amounts of ischemic myocardium in these two groups. The available studies have utilized planar thallium-201 exercise and redistribution imaging. There are no data employing single photon emission computed tomographic (SPECT) thallium-201 imaging which, by virtue of improved sensitivity in the demonstration of ischemia in individual coronary artery distributions and its ability to display the myocardium in three dimensions, is more ideally suited for evaluation of jeopardized myocardium.

It is the purpose of this study to compare the amount of ischemic myocardium, utilizing SPECT thallium-201 exercise and redistribution imaging, in patients experiencing angina during treadmill testing and in those who had ischemia during exercise without associated anginal pain (that is, silent ischemia).

Methods

Study patients. The study group consisted of 112 consecutive patients with coronary artery disease undergoing coronary arteriography who had exercise and redistribution thallium-201 tomographic imaging demonstrating ischemia (see later) within a 1 month period. Eighty-four patients terminated exercise because of shortness of breath or fatigue without experiencing anginal pain and were characterized as having silent ischemia; 28 patients experienced angina and were classified as having painful ischemia.

Exercise protocol and imaging procedure. All patients underwent standard Bruce protocol exercise testing (12) to a symptom-limited maximum. Standard 12 lead electrocardiographic (ECG) tracings were considered positive if there was ≥1 mm of horizontal or downsloping ST depression for

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Manuscript received October 14, 1988; revised manuscript received March 27, 1989, accepted April 19, 1989.

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0735-1097/89/$3.50

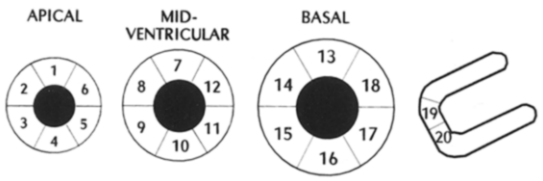

Figure 1. Division of SPECT myocardial images into 20 myocardial segments. Anterior = 1, 7, 13; anteroseptal = 2, 8, 14; inferoseptal = 3, 9, 15; inferior = 4, 10, 16; inferolateral = 5, 11, 17; anterolateral = 6, 12, 18; anteroapical = 19; inferoapical = 20.

≥0.08 s after the J point compared with the rest tracing. Four patients, three with silent ischemia and one with painful ischemia, had baseline abnormalities that precluded analysis of further ST segment changes with exercise and were excluded from comparisons of ischemic segments in those with a positive versus negative exercise ECG. Three millicuries of thallium-201 was injected 1 min before the termination of exercise. SPECT images were obtained 10 min after isotope injection and 3 to 5 h later with use of a Siemens Orbiter large field of view tomographic camera interfaced with a Medical Data Systems A^3 computer. The camera was equipped with 75 photomultiplier tubes, a 0.25 in. (0.64 cm) thick sodium iodide crystal and an all purpose parallel hole collimator. A 20% energy window was positioned on the 80 keV photopeak and a second 15% energy window was centered on the high energy peak of thallium-201. Thirty-two equidistant projections were obtained for 40 s each over a 180° rotation from the 45° right anterior oblique to the 45° left posterior oblique position and were stored on magnetic disc with use of a 64 × 64, 16 bit matrix.

Each of the 32 projections was corrected for nonuniformity with a cobalt-57 source, collecting 30 million counts. The mechanical center of rotation was determined to align the detector data with respect to the reconstruction matrix and to monitor gantry stability. The raw data were smoothed with use of a 9 point weighted averaging system. Filtered back projection was performed with use of a Butterworth filter with a cutoff frequency of 0.2 cycle/pixel and order 5. Tomograms were reoriented in the short-axis and vertical long-axis planes and reconstructed at 1 pixel/slice, representing approximately 6.2 mm thickness. The short-axis slices were analyzed from the subendocardial portion of the apex to the base of the heart and the long-axis slices from the subendocardial portion of the septum to the subendocardial portion of the lateral wall. Short-axis slices were divided into six equal segments (anterior, anteroseptal, inferoseptal, inferior, inferolateral and anterolateral) at apical, mid and basal ventricular levels. The apical portion of the vertical long-axis slices was divided into anterior and inferior segments, resulting in a total of 20 segments/patient (18 from the short- and 2 from the vertical long-axis views) without duplication of the same anatomic area on different projections (Fig. 1).

Table 1. Characteristics of Patients

	Silent Ischemia	Painful Ischemia
No. of patients	84	28
Age (yr)	59.4	57.8
Male	88%	89%
Female	12%	11%
Diabetes mellitus	13%	32%*
History of anginal pain	90.5%	100%
Prior myocardial infarction	39%	54%
Antianginal drugs	87%	75%
Nitrates	46%	61%
Calcium channel blockers	79%	75%
Beta-adrenergic blockers	18%	14%
Digoxin	12%	14%

*$p < 0.05$.

Qualitative analysis of each segment of the exercise and redistribution views was performed on a 0 to 4 scale (0 = normal, 1 = equivocally reduced thallium uptake, 2 = mildly reduced uptake, 3 = moderately reduced uptake, 4 = severely reduced uptake) by two independent observers without knowledge of catheterization data. Scores of ≥2 were considered abnormal and differences of opinion were resolved by consensus. Quantitative analysis of the same segments was performed (13) and was used for confirmation of visual analysis. In our laboratory, the specificity of SPECT imaging for detecting silent ischemia in normal patients, defined as those having <3% likelihood of disease by Bayesian analysis, is 88%.

Ischemia was categorized as either total or partial normalization of a segment from exercise to redistribution imaging with a minimal improvement of 1 point on the visual scale.

Coronary arteriography. All patients underwent selective coronary arteriography within 1 month of the SPECT exercise imaging. Selective left and right coronary arterio-

Table 2. Exercise Performance in 112 Patients

	Silent Ischemia	Painful Ischemia
No. of patients	84	28
Positive exercise ECG	32%	70%*
Achieved ≥85% predicted maximal heart rate	63%	43%
Exercise duration (min)	7.1 ± 2.8	6.2 ± 1.7†
METS achieved	9.4 ± 2.7	8.5 ± 1.9‡
Peak heart rate (beats/min)	138 ± 20	132 ± 22
Peak systolic blood pressure (mm Hg)	167 ± 25.5	170 ± 21
Peak rate-pressure product (heart rate × BP)	23,300 ± 5,744	22,408 ± 4,601

*$p < 0.001$; †$p = 0.07$; ‡$p < 0.05$. BP = blood pressure; ECG = electrocardiogram; METS = metabolic equivalent.

Table 3. Coronary Arteriography in the Two Patient Groups

	Silent Ischemia (%)	Painful Ischemia (%)
Single vessel disease	44	50
Double vessel disease	34	21
Triple vessel disease	22	29
Coronary artery involved		
Left anterior descending	41	34
Right	29	40
Left circumflex	30	26

Table 4. SPECT Evaluation of Ischemic Segments in Silent vs. Painful Ischemia

	Number of Ischemic Segments/Patient	
	Silent Ischemia (%)	Painful Ischemia (%)
Partial or total redistribution	7.4 ± 4.7	7.6 ± 3.7
Total redistribution	4.7 ± 3.6	5.4 ± 3.4

grams were obtained with either the Judkins or the Sones approach.

Analysis. Statistical analyses were performed with the Student's *t* test and chi-square analysis. The data were analyzed retrospectively.

Results

Patient characteristics and exercise performance (Tables 1 and 2). There were no significant differences in the age and gender distribution of the two patient groups. The silent ischemia group had a significantly lower proportion of patients with diabetes mellitus than did the painful ischemia group (13.1% versus 32.1%, $p < 0.05$); the distribution of insulin dependence and diabetic neuropathy was similar within the two groups. Angina was the presenting symptom in 92.9% of patients and there was no significant difference in the frequency of anginal history or prior myocardial infarction between the silent and painful ischemia groups. Similar proportions of both groups were taking nitrates, calcium channel and beta-blocking drugs and digoxin. The silent ischemia group had a significantly lower incidence of positive exercise ECG findings ($p < 0.001$) with a higher level of metabolic equivalent (METS) achieved ($p < 0.05$) and slightly longer exercise duration ($p = 0.07$). There were no differences in peak heart rate, systolic blood pressure or double (rate-pressure) product.

Coronary arteriography (Table 3). There was a similar incidence of single, double and triple vessel disease in the silent and painful ischemia groups and there were no significant differences between groups in the distribution of disease in the left anterior descending, right coronary and left circumflex coronary arteries.

SPECT imaging (Tables 4 to 6). In the silent ischemia group (Table 4), of a possible total of 20 segments, 7.4 ± 4.7 segments demonstrated some degree of ischemic redistribution with 4.7 ± 3.6 segments normalizing totally. In the painful ischemia group, 7.6 ± 3.7 segments demonstrated ischemic redistribution with 5.4 ± 3.4 segments displaying total normalization. There were no statistically significant differences between the two groups. Patients with positive and negative exercise ECG findings (Table 5) had similar numbers of ischemic segments irrespective of associated silent or painful ischemia.

The distribution of ischemic segments in the silent and painful ischemia groups is shown in Table 6. Of the seven anatomic areas, only the inferolateral wall demonstrated any significant difference between the two groups.

Examples of silent and painful ischemia are demonstrated in Figures 2 and 3. Similar amounts of ischemic myocardium are demonstrated in the distribution of the left anterior descending artery with a proximal 90% stenosis in the absence of angina and ECG changes (Fig. 2) and in the presence of angina and ST depression (Fig. 3).

Discussion

This study clearly demonstrates comparable amounts of ischemic myocardium in patients who exercised without anginal pain (i.e., silent ischemia) and those who experienced angina with treadmill exercise.

Clinical patterns. Seventy-five percent of a consecutive series of patients exercised without anginal pain despite a history of prior angina, demonstrated by SPECT imaging.

Table 5. SPECT Evaluation of Ischemic Segments in Patients With Positive (Pos.) Versus Negative (Neg.) Exercise ECG Findings

	All Patients		Silent Ischemia		Painful Ischemia	
	Exercise ECG		Exercise ECG		Exercise ECG	
	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
No. of patients	45	63	26	55	19	8
Number of ischemic segments/patient						
Partial or total redistribution	7.6 ± 4.2	7.4 ± 3.7	7.7 ± 4.8	7.3 ± 3.6	7.4 ± 3.3	8.2 ± 4.7
Total redistribution	5.2 ± 3.7	4.7 ± 3.5	5.2 ± 3.9	4.5 ± 3.5	5.3 ± 3.3	5.7 ± 3.6

Table 6. Distribution of Ischemic Segments in Silent Versus Painful Ischemia

	Silent Ischemia (%)	Painful Ischemia (%)
Anterior	13	12
Anteroseptal	14	11
Inferoseptal	17	12
Inferior	26	29
Inferolateral	12	18*
Anterolateral	9	7.5
Apical	9.5	10

*$p < 0.05$.

This percentage is higher than previously reported data ranging from 48% to 57% (3,7,14) for exercise-induced ischemia and similar to the 60% to 91% range for silent spontaneous episodes detected by ST segment ambulatory ECG (Holter) monitoring (2,15,16). Because the mechanism of silent ischemia is not understood, the reason for the higher percentage of exercise-induced silent ischemia in this study is not clear.

The clinical characteristics of the silent and painful ischemia groups (Table 1) were similar except for a lesser incidence of diabetes mellitus in the silent ischemia group (13.1% versus 32.1%). Previous reports (14,17) have found an equal or higher incidence of diabetes in patients with silent ischemia but used ECG criteria alone for defining ischemia as opposed to the thallium-201 myocardial perfusion criteria in this study. When our data are analyzed in a similar manner, i.e., limiting evaluation to patients with positive exercise ECG findings and excluding those with negative exercise ECG findings, there were no significant differences in either the incidence of diabetes in the silent and painful ischemia groups (19% versus 32%) or in the incidence of silent ischemia in patients with and without diabetes (45% versus 62%); these findings are in agreement with the data of Chipkin et al. (14). The number of patients with negative exercise ECG findings in the painful ischemia group was too small to allow for valid comparison and, therefore, conclusions cannot be made about the incidence of diabetes in this subgroup.

Almost all patients in both groups had a past history of angina and a similarly high proportion were taking antianginal medications. The silent ischemia group had a slightly longer exercise duration and achieved a higher METS level, perhaps because they were not limited by chest pain. However, there were no significant differences between groups in peak heart rate, blood pressure and rate-pressure product. Nonetheless, the incidence of positive ECG responses to exercise was lower in the silent ischemia group than in the painful ischemia group (31% versus 68%, $p < 0.001$). Assey et al. (7), in the only other study using thallium-201 perfusion criteria, reported a similar low incidence of positive ECG responses to exercise in silent ischemia (41%) and a lower

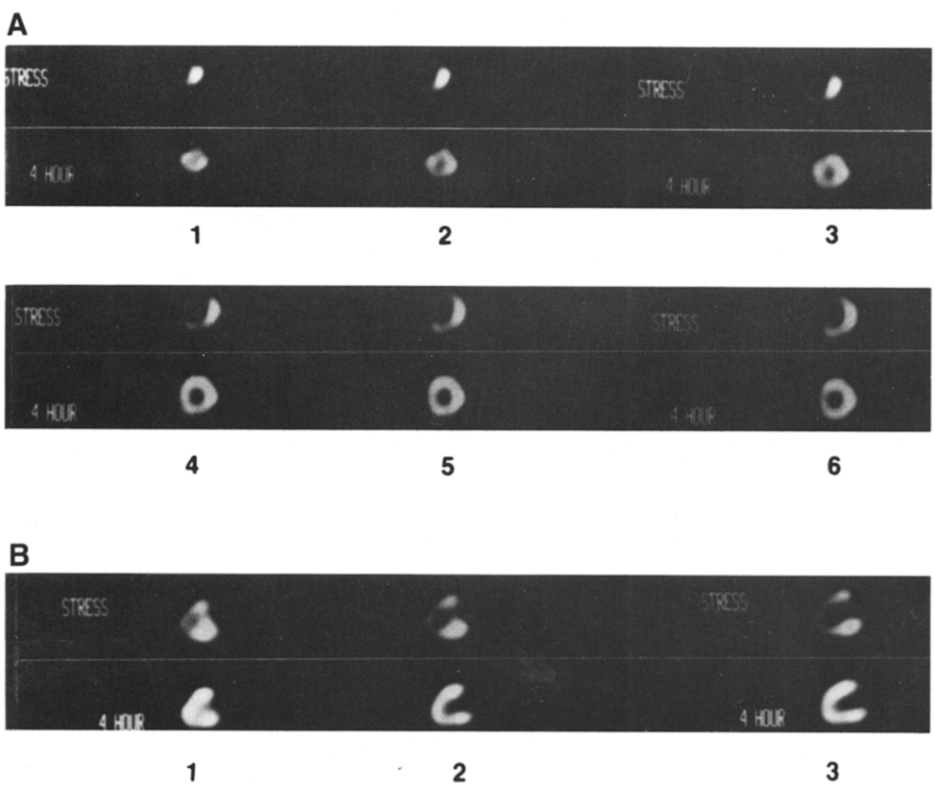

Figure 2. SPECT images during exercise and at 4 h after exercise demonstrating silent ischemia. **A**, Short-axis view. Reversible anterior, anteroseptal, inferoseptal and inferior defects at all levels (segments 1 to 6 progress from apex to base). **B**, Vertical long-axis view. Reversible anteroapical and inferoapical defects (segments 1 to 3 progress from septal to lateral surfaces). Coronary arteriography demonstrated 90% stenosis of the proximal left anterior descending coronary artery.

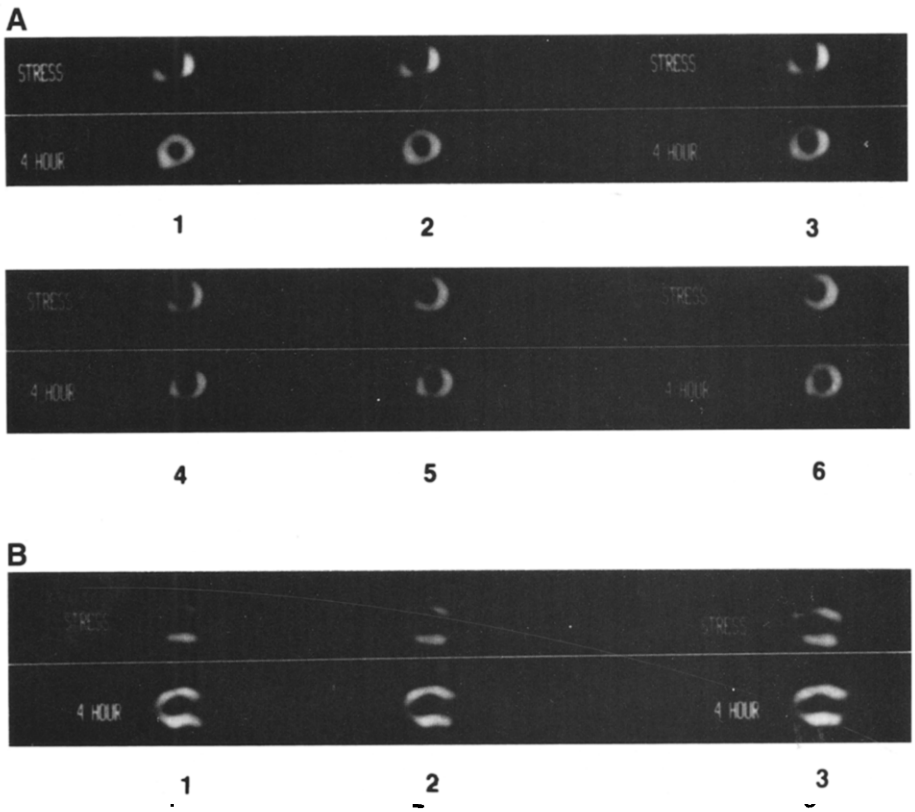

Figure 3. SPECT images during exercise and at 4 h after exercise demonstrating Ischemia accompanied by angina. **A**, Short-axis view. Reversible anteroseptal, inferoseptal and inferior defects at apical and midventricular levels with partial septal reversibility at the base; reversible anterior defect at the apex with partial reversibility at midventricular and basilar levels (segments 1 to 6 progress from apex to base. **B**, Vertical long-axis view. Partially reversible anteroapical and inferoapical defects (segments 1 to 3 progress from septal to lateral surfaces. Coronary arteriography demonstrated 90% stenosis of the proximal left anterior descending artery.

incidence of positive responses in the painful ischemia group (50%), utilizing an identical exercise protocol.

The mechanism responsible for the low incidence of positive ECG findings in silent ischemia is not evident from this study. The association of absence of both exercise-induced ECG changes and anginal pain in patients, almost all of whom have experienced anginal pain in the past, may reflect a temporal variation in as yet undetermined mediators of a common pathway responsible for both the ECG and pain response to the ischemic stimulus of relative myocardial hypoperfusion.

Coronary angiography. The distribution of single, double and triple vessel disease was similar in the two groups (Table 3), a finding consistent with prior reports (1–7). There are no previously published data regarding the incidence of disease of the left anterior descending, left circumflex and right coronary arteries. In this study, the distribution of disease in individual vessels was similar in the silent and painful ischemia groups.

SPECT thallium-201 imaging. This is the first study utilizing SPECT thallium-201 imaging to compare the amount of ischemic myocardium in silent and painful ischemia. Deanfield et al. (18) found similar patterns of decreased rubidium-82 uptake by positron emission tomography in patients with angina and ST depression and in those with silent ST depression accompanying exercise or cold pressor test or without provocation. Reisman et al. (10,11), in preliminary work utilizing planar thallium-201 imaging, found comparable amounts of ischemia in patients with silent and painful ischemia despite a higher incidence of multivessel disease in the silent ischemia group (10); they noted a similar amount of ischemic myocardium and number of cardiac events in patients with silent and painful ischemia achieving <85% of predicted maximal heart rate (11).

SPECT imaging, with its three-dimensional ability to examine the myocardium at different levels from apex to base and from septal to lateral surfaces, appears much more suited for evaluation of the amount of jeopardized ischemic myocardium than does conventional planar imaging with its potentially misleading two-dimensional representation of a three-dimensional structure. Moreover, SPECT imaging has been shown (19,20) to be more accurate for evaluation of ischemia in the distribution of the left circumflex coronary artery.

The present study, utilizing SPECT imaging in a nonselected series of patients with comparable clinical characteristics and angiographic extent of coronary disease, clearly demonstrates similar amounts and distribution of jeopardized ischemic myocardium during treadmill testing whether or not there is accompanying angina or exercise-induced ST depression (Tables 4 to 6). Of the seven anatomic areas, only the inferolateral segment had a different incidence of silent ischemia, without apparent explanation.

Significance of presence or absence of ECG change in silent ischemia. In light of the comparable amounts of ischemia, the similar prognosis of patients with and without angina reported by most investigators (1–6,9,10) is not surprising because in the final analysis, it should be the amount of myocardium at risk that determines survival. Moreover, all published reports, with the exception of that of Assey et al. (7), have used the presence or absence of ST depression to define ischemia and have excluded from consideration those patients without ST depression. The present study (Table 5) demonstrates that the amount of ischemic myocardium is similar in patients with and without exercise-induced ST depression. Consequently, studies that have relied solely on ECG criteria have probably greatly underestimated the number of patients with silent ischemia. The use of ST segment Holter monitoring (2,15,16,18) to evaluate nonexercise-induced ischemia, by relying solely on ECG changes, may also underestimate the incidence of silent ischemia if the results of our present exercise study can be extrapolated to spontaneous ischemia.

Clinical implications. This study supports a greater role for SPECT imaging in the evaluation of myocardial ischemia and suggests that physicians should give greater weight to the amount of jeopardized myocardium in the decision-making process rather than rely strictly on symptoms and angiographic extent of coronary disease. The data highlight the false sense of security that may follow conventional exercise ECG testing not accompanied by angina and ST depression, as evidenced by the 68% of patients in the silent ischemia group who had no ST depression. Finally, because the majority of patients with silent ischemia in this study and that of Assey et al. (7) had no ST depression, future evaluation of this important syndrome should employ SPECT imaging, which, by extension of our results, would identify an even greater number of patients experiencing silent ischemia than has been previously appreciated.

We acknowledge the help of Steve Lugon in typing the manuscript.

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