Altered Myocardial Perfusion in Patients With Angina Pectoris or Silent Ischemia During Exercise as Assessed by Quantitative Thallium-201 Single-Photon Emission Computed Tomography

John J. Mahmanian, MD, Craig M. Pratt, MD, Mary K. Cocanougher, BS, and Mario S. Verani, MD

The extent of abnormally perfused myocardium was compared in patients with and without chest pain during treadmill exercise from a large, relatively low-risk consecutive patient population (n=356) referred for quantitative thallium-201 single-photon emission computed tomography (SPECT). All patients had concurrent coronary angiography. Patients were excluded if they had prior coronary angioplasty or bypass surgery. Tomographic images were assessed visually and from computer-generated polar maps. Chest pain during exercise was as frequent in patients with normal coronary arteries (12%) as in those with significant (>50% stenosis) coronary artery disease (CAD) (14%). In the 219 patients with significant CAD, silent ischemia was fivefold more common than symptomatic ischemia (83% versus 17%, p=0.0001). However, there were no differences in the extent, severity, or distribution of coronary stenoses in patients with silent or symptomatic ischemia. Our major observation was that the extent of quantified SPECT perfusion defects was nearly identical in patients with (20.9±15.9%) and without (20.5±15.6%) exertional chest pain. The sensitivity for detecting the presence of CAD was significantly improved with quantitative SPECT compared with stress electrocardiography (87% versus 65%, p=0.0001). Although scintigraphic and electrocardiographic evidence of exercise-induced ischemia were comparable in patients with chest pain (67% versus 73%, respectively; p=NS), SPECT was superior to stress electrocardiography for detecting silent myocardial ischemia (52% versus 35%, respectively; p=0.01). The majority of patients in this study with CAD who developed ischemia during exercise testing were asymptomatic, although they exhibited an angiographic profile and extent of abnormally perfused myocardium similar to those of patients with symptomatic ischemia. The prognostic significance of quantified perfusion defects detected by SPECT remains to be assessed. (Circulation 1990;82:1305–1315)

Since the original description of asymptomatic myocardial ischemia in patients with coronary artery disease, there has been a rapid expansion of the literature regarding silent ischemia to better define its clinical relevance. Various electrocardiographic and scintigraphic techniques have contributed to developing a unified concept of the pathophysiological and prognostic implications of silent ischemia. When assessed by ambulatory electrocardiographic monitoring, episodes of asymptomatic ST segment depression are frequent1-5 and are accompanied by both scintigraphic5,6 and hemodynamic changes7-10 consistent with myocardial ischemia. Furthermore, the presence of ST segment depression during Holter monitoring predicts future cardiac events in patients who have unstable angina11 or recent myocardial infarction.12 The presence of reversible perfusion defects during exercise scintigraphy in asymptomatic13 and symptomatic14 patients and in those with multivessel coronary artery

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disease or recent myocardial infarction is clearly associated with a poor outcome. There are few available data, however, on whether the development of chest pain during exercise identifies coronary artery disease patients with a greater extent of myocardial ischemia when compared with asymptomatic patients. This is primarily due to the lack of precise techniques in the past for accurately detecting and quantifying the extent of ischemia.

Single-photon emission computed tomography (SPECT) is a highly sensitive and specific imaging technique currently available for detecting exercise-induced reversible abnormalities in myocardial perfusion. In the present study, reversible perfusion defects were defined as indicating ischemia, although there is only indirect evidence in the literature to support this contention. Tomographic imaging of the heart also allows accurate quantification of myocardial perfusion defects. Our quantification technique has been validated in cardiac phantoms, in models of experimental infarction in animals by using a technetium-isonitrite tracer, and in humans when compared with creatine kinase–MB infarct sizing. Therefore, SPECT appears to be ideally suited for elucidating the relative extent of myocardial perfusion defects, whether symptomatic or silent.

Accordingly, this prospective investigation was designed to determine whether patients with, compared to those without, chest pain during exercise treadmill testing differ in frequency and extent of reversible perfusion defects as assessed by quantitative thallium-201 SPECT.

Methods

Patients

The study population comprised 356 consecutive patients (265 men and 91 women; mean age, 56±10 years; age range, 29–83 years) referred for exercise 201TI SPECT. Patients with prior percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery were excluded. All patients had coronary angiography either before (mean, 5.1±7.8 days) or after (mean, 2.8±7.2 days) SPECT. Significant coronary artery disease, defined as more than 50% luminal diameter stenosis in at least one major coronary vessel, was found in 219 patients. Seventy-three patients had normal coronary arteries, whereas 64 had insignificant coronary artery disease (26–50% stenosis). Coronary angiography revealed one-vessel disease in 141 patients (64%), two-vessel disease in 64 patients (29%), and three-vessel disease in 14 patients (7%).

Most patients had a history of chest pain (67%), either typical (50%) or atypical (17%) for angina; less common symptoms were dyspnea (8%), palpitations (3%), and dizziness (2%). Eighteen percent of the patients were entirely asymptomatic and were referred for SPECT evaluation because of the presence of coronary risk factors or a positive treadmill test. In the 219 patients with coronary artery disease, 86 (39%) did not have prior myocardial infarction, whereas 74 (34%) had a definite infarction. Fifty-nine patients (27%) had questionable infarction with either historical or electrocardiographic (diagnostic Q waves) evidence of infarction, but not both. At the time of cardiac imaging, many of the 219 patients with documented coronary artery stenosis were on antianginal medications consisting of nitrates (n=86), β-blockers (n=63), and calcium antagonists (n=101). Seventy-eight patients (36%) were on at least two cardiac medications.

Exercise Protocol

All patients underwent symptom-limited treadmill exercise using the Bruce protocol. Blood pressure, heart rate, and a 12-lead electrocardiogram were recorded at 1-minute intervals, with the latter monitored continuously throughout the study. An ischemic electrocardiographic response was considered present if 1-mm or more horizontal or downsloping ST segment depression occurred, measured at 0.08 second after the J point. An infarction pattern was considered present on the rest electrocardiogram when diagnostic Q waves were present in the appropriate anterior, inferior, or lateral leads. Criteria routinely used in our laboratory for the early termination of exercise are severe dyspnea, hypotensive response, marked ST segment depression (≥3 mm), or onset of ventricular tachycardia, although none of the patients in the present study developed such complications. The development of chest pain during exercise was not an absolute indication for termination of the stress test unless accompanied by marked ST segment depression or considered intolerable by the patient. At peak exercise, 3 mCi 201TI was injected intravenously and flushed with saline solution. The patients were then encouraged to exercise for an additional 30–60 seconds after the radionuclide injection.

Analysis of Exercise Electrocardiograms

In order to develop a composite score for evaluating the severity of ischemic electrocardiographic changes during exercise, four variables were analyzed: 1) development of an ischemic (≥1 mm) ST segment depression, 2) time elapsed from the beginning of exercise until ischemic response (≤3 versus >3 minutes), 3) recovery time after termination of exercise for ST normalization (>3 versus ≤3 minutes), and 4) number of leads involved (more than three versus three or less). The variables were scored as either 0 (absent) or 1 (present) with a maximal total score of 4 indicating an electrocardiogram strongly positive for ischemia.

SPECT

SPECT was initiated within 5 minutes of terminating exercise with a large field-of-view, single-crystal, rotating gamma camera (ADAC ARC 3000-3300) equipped with a high-resolution, parallel hole collimator with a septal length and thickness of 33 and
0.15 mm, respectively. Image acquisition was performed over an 180° arc from the 45° left posterior oblique to the 45° right anterior oblique position, at 6°-intervals, and for 40 seconds per image. Images were acquired on a 64x64x8 byte matrix and subsequently stored on a two-gigabyte laser disk for further analysis.

Transaxial reconstruction involved a back-projection technique with a Butterworth (order, 5) high-pass filter with a low-pass window at a 50% cutoff. Reconstructed tomographic slices of 6-mm thickness were then reoriented in the standard short, horizontal long, and vertical long axes for visual and quantitative analyses. Redistribution images were obtained 4 hours after exercise.

**Visual Analysis of Tomographic Slices**

Visual assessment of all tomographic slices was performed by one experienced investigator blinded to the coronary angiographic results. The slices were displayed sequentially on a large, color oscilloscope; perfusion defects in each vascular territory were assessed in all three cardiac planes. Perfusion defects were analyzed for the presence of complete or partial redistribution (reversibility) or no redistribution (scar) 4 hours after 201TI injection. Undoubtedly, the extent of reversibility is underestimated using such a definition because delayed redistribution (24 hours) is known to occur quite often.23

The vascular territories of the three major coronary arteries were assigned as follows: anteroseptal, anterior, and anterolateral walls to the left anterior descending coronary artery; inferior, posterior, and posteroseptal walls to the right coronary artery; and lateral and posterolateral walls to the circumflex coronary artery. Pure apical defects were considered indicative of coronary artery disease but could not be assigned to a particular coronary artery due to the well-recognized vascular overlap that occurs at the apex.

In a randomly selected group of 51 patients with significant coronary artery disease, we determined the intraobserver and interobserver reproducibilities for detecting the presence and localizing the site of reversible exercise perfusion defects. The interobserver reproducibility was determined by a second expert nuclear cardiologist who independently reinterpreted the images. The intraobserver reproducibility was determined by the original interpreter who reanalyzed the images at least 3 months after the original readings.

**Computer Quantification of Tomographic Images**

The 201TI tomographic images were quantified from computerized two-dimensional polar maps of the three-dimensional myocardial radioactivity. The maps were generated with a circumferential profile analysis previously validated in our laboratory,22 whereby pixel count activity from the center to the outer boundary of each short-axis slice was determined along radians spaced at 6° intervals over 360°.

The count activity for each radian was determined as the maximal three-point average along the radian, which was then normalized to the three consecutive pixels with the highest average activity within the slice. The individual slices from cardiac apex to base were displayed in the polar map as concentric rings from the center to the periphery of the map. The septal and lateral left ventricular apical limits were defined from the midcavitary short-axis slice, and the apical count activity was determined from each 6-mm-thick vertical long-axis slice found within these limits. The apical activity was then displayed in the center of the polar map. This method has been described in detail.22

The map of each patient was statistically compared with a normal data base previously generated in our laboratory. This normal data base consisted of 50 individuals (23 men and 27 women; mean age, 50 years; range, 26–69 years) who may have had normal coronary arteriograms but were all at low risk (<2% likelihood) for coronary artery disease in that they had nonanginal chest pain, no prior cardiovascular history, normal resting electrocardiograms and less than three cardiac risk factors, and had achieved more than 85% of their predicted heart rate on the stress electrocardiogram without development of ischemic changes or angina. Separate normal data bases that depended on exercise intensity were not used; although absolute myocardial thallium concentrations increase with exercise intensity, the relative regional uptake of thallium in the normal heart does not vary significantly from rest to exercise.24,25 Likewise, separate data bases for men and women were not used; experience with our methods of acquisition, processing, and quantification has resulted in no significant observed differences in detection or quantification of perfusion defects for gender-specific versus mixed-gender data bases.22 A pixel in the patient's polar map was considered abnormal if its count activity decreased more than 2.5 SDs below the mean count for the corresponding pixel in the normal data base. Quantitative 201TI tomographic defect size was then expressed as the percentage of abnormal pixels in the total polar map.

Designation of coronary vascular territories was identical to that used for visual analysis of tomographic slices. The patient's polar map was considered abnormal if a 3% or more focal perfusion defect was found within a given vascular territory. This criterion has led to a high sensitivity for detecting coronary artery disease, both in individual patients and in all three coronary vascular territories, while maintaining a high specificity.26 Furthermore, interobserver and intraobserver reproducibility for computer-generated perfusion defect size in our laboratory has been shown to be excellent (r=0.98).26

The quantitative polar maps were used to assess the presence and extent of coronary artery disease. The degree to which the initial exercise perfusion defects were reversible, however, was decided primarily from the visual analysis of the individual
tomographic slices. This was necessary because the normal data base redistribution and washout counts were based on a population achieving maximal exercise and could not be properly extrapolated to many of our patients, who achieved less than 85% of their predicted heart rate and consequently might have had different $^{31}Tl$ washout rates. In our experience, the visual and quantitative methods have been shown to detect coronary artery disease with a similar high sensitivity (87%), although the latter tends to enhance specificity (76% versus 87%, respectively).26

Coronary Angiography

Selective coronary cineangiography was performed in multiple views with standard techniques. Coronary stenoses were measured with calipers by an experienced angiographer blinded to the scintigraphic results and expressed as percent luminal diameter stenosis. Stenosis severity was graded in the following manner: normal ($\leq 25\%$ stenosis), insignificant (26–50\% stenosis), moderate (51–69\% stenosis), and severe ($\geq 70\%$ stenosis). The interobserver reproducibility of this method was determined in 51 randomly selected patients with coronary artery disease by having a second expert angiographer independently analyze the arteriograms.

Statistics

The comparison of baseline characteristics, exercise parameters, coronary angiographic findings, and perfusion defect sizes of patients with (group 1) and without (group 2) exertional chest pain was performed with unpaired $t$ tests. When a normal distribution was not present, the Wilcoxon rank-sum test was used.

$\chi^2$ analysis was used to compare the frequency and location of scintigraphic redistribution in group 1 and group 2 patients and to compare the ability of SPECT with that of electrocardiography to detect coronary artery disease and the presence of ischemia. Correlations between the tomographic perfusion defect size and the electrocardiographic ischemia score were performed with linear regression analysis. Linear regression analysis was also used to determine the interobserver reproducibility for estimating individual coronary artery stenosis and the reproducibility of SPECT for quantifying perfusion defects. Values are given as mean±SD. A $p$ value of less than 0.05 was considered significant.

Results

Baseline Characteristics and Exercise Results

Chest pain during treadmill exercise was infrequent and occurred in only 52 of the 356 patients (15\%) studied. Among those with normal coronary arteries or insignificant stenoses, nine of 73 (12\%) and 13 of 64 (20\%) patients, respectively, developed exertional chest discomfort. One of the nine patients with normal coronary arteries (11\%) and six of the 13 patients with insignificant stenoses (46\%) had both exertional chest pain and an abnormal SPECT study. Only 30 of the 219 patients (14\%) with significant coronary artery stenosis developed chest discomfort during exercise, whereas 189 patients (86\%) did not. The prevalence of chest pain was not significantly different among any of these patient groups.

The 219 patients with significant coronary artery disease are the focus of all subsequent analysis. Baseline characteristics (Table 1) were similar for patients with (group 1) and without (group 2) exertional chest pain, although $\beta$-blocking drugs were more frequently prescribed for group 1 patients. Although most patients were on cardiac medications (164 of 219, or 75\%) at the time of imaging, exertional chest discomfort occurred as frequently ($p=NS$) in medicated (23 of 164, or 14\%) as in nonmedicated (seven of 55, or 13\%) patients.

Exercise parameters are given in Table 2. Although exercise time and peak blood pressures did not differ between the two groups, group 2 patients achieved a higher percent target and absolute heart rate, and double product than those in group 1. Furthermore, 54\% of group 2 but only 33\% of group 1 patients achieved 85\% or more of their predicted heart rate ($p<0.05$). Similar observations were noted between the two groups for patients on and off cardiac medications at the time of exercise testing.

Coronary Angiographic Results

In the 219 patients who had coronary artery disease, no significant differences in the extent, distribution, or severity of stenoses were observed between the two groups (Table 3). The frequencies of one-vessel and multivessel disease in group 1 (67\% and 33\%, respectively) and group 2 (64\% and 36\%, respectively) patients were comparable ($p=NS$). Furthermore, the distribution of one-, two-, and three-vessel disease associated with each coronary artery was also similar: left anterior descending (46\%, 39\%, and 15\%), right (49%, 41%, and 10%), and circumflex (38\%, 44\%, and 18\%) coronary arteries, respectively ($p=NS$). Individual vessel analysis revealed a remarkably similar distribution and severity of significant (>50\%) stenoses of the left anterior

<table>
<thead>
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<th>Table 1. Baseline Characteristics</th>
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<tr>
<td>Age (yr)</td>
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<tr>
<td>55±9.5</td>
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<tr>
<td>Men/women</td>
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<tr>
<td>Previous myocardial infarction (%) (%)</td>
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<tr>
<td>Medications (%)</td>
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<tr>
<td>Nitrates</td>
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<tr>
<td>Ca$^{2+}$ blockers</td>
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<tr>
<td>$\beta$-blockers</td>
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<tr>
<td>Two or more</td>
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*p=0.035 vs. group 2.

Group 1, patients with exercise-induced chest pain; group 2, patients without exercise-induced chest pain.
TABLE 2. Exercise Parameters

<table>
<thead>
<tr>
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<th>Overall</th>
<th>Medications</th>
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<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 1</td>
</tr>
<tr>
<td></td>
<td>(n=30)</td>
<td>(n=189)</td>
<td>(n=23)</td>
</tr>
<tr>
<td>Exercise time (min)</td>
<td>6.8±2.3</td>
<td>7.1±2.3</td>
<td>6.8±2.3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>127±19</td>
<td>142±21*</td>
<td>126±20</td>
</tr>
<tr>
<td>Target heart rate (%)</td>
<td>77±11</td>
<td>84±12†</td>
<td>78±12</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>157±25</td>
<td>160±25</td>
<td>153±19</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>85±13</td>
<td>86±16</td>
<td>82±11</td>
</tr>
<tr>
<td>Double product (heart rate x systolic blood pressure)</td>
<td>19,998±4,822</td>
<td>22,859±5,612*</td>
<td>19,370±4,537</td>
</tr>
</tbody>
</table>

* p<0.01 vs. group 1; † p<0.05 vs. group 1; § p<0.05 vs. medications (group 2); $ p<0.05 vs. medications (group 1).

descending, right coronary, and circumflex coronary arteries in the two patient groups.

Interobserver agreement for measuring the angiographic severity of stenosis was determined in 51 patients with stenoses ranging from 0% to 100%. In vessels defined as normal or having only insignificant stenoses and in vessels defined as having significant (>50%) stenoses, the interobserver agreements were 96% (73 of 76) and 99% (76 of 77), respectively. Furthermore, interobserver agreement was 84% (65 of 77) when vessels were further classified as having either moderate (51–69%) or severe (≥70%) stenosis. The paired mean stenosis severities for vessels with more than 50% occlusion were 84.5±14.8% (observer 1) compared with 84.4±16.2% (observer 2). Likewise, the mean absolute differences in percent diameter stenosis between the two observers were small (7.3±8.7%; median, 4%). Linear regression analysis between the measured percent stenoses by the two observers yielded correlation coefficients of 0.95 (stenosis severity1=0.34+0.99×stenosis severity2; p<0.0001) for all vessels and 0.77 (stenosis severity1=18.1+0.77×stenosis severity2; p<0.0001) for those with more than 50% stenosis.

Reproducibility of Quantitative and Visual SPECT Analysis

The intraobserver and interobserver reproducibilities for SPECT in quantifying perfusion defects and visually detecting the presence and site of scintigraphic reversibility were determined in a random group of 51 patients with significant coronary artery disease who had scintigraphic perfusion defects ranging from 0% to 73%.

The paired perfusion defect sizes by quantitative tomographic analysis were 23.5±16.0% compared with 22.9±15.4% (p=NS) when measured by the same observer and 22.9±15.4% compared with 22.9±15.8% (p=NS) when measured by two observers. The absolute mean intraobserver and interobserver differences for computer-quantified perfusion defect sizes were small (3.3±3.5% and 3.8±3.1%, respectively). Linear regression analysis yielded correlation coefficients of 0.95 (defect size1=1.23+0.92×defect size2; p<0.0001) and 0.95 (defect size1=0.69+0.97×defect size2; p<0.0001) for the intraobserver and interobserver comparisons, respectively.

The interobserver and intraobserver agreements for visually identifying patients with reversible perfusion defects by scintigraphy were 80% and 88%, respectively. Most of the disagreements (88%) were confined to patients classified as showing either no redistribution or partial redistribution of an exercise perfusion defect. The interobserver and intraobserver agreements for identifying the coronary artery corresponding to each perfusion defect were 90% and 94%, respectively.

TABLE 3. Coronary Angiographic Findings

<table>
<thead>
<tr>
<th>Coronary disease extent (n) (%)</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
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<tbody>
<tr>
<td>One-vessel disease</td>
<td>20/30 (67)</td>
<td>121/189 (64)</td>
</tr>
<tr>
<td>Two-vessel disease</td>
<td>8/30 (27)</td>
<td>56/189 (30)</td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>2/30 (6)</td>
<td>12/189 (6)</td>
</tr>
<tr>
<td>Vessel distribution (&gt;50% stenosis) (n) (%)</td>
<td></td>
<td></td>
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<tr>
<td>LAD</td>
<td>13/42 (31)</td>
<td>84/269 (31)</td>
</tr>
<tr>
<td>RCA</td>
<td>15/42 (36)</td>
<td>120/269 (45)</td>
</tr>
<tr>
<td>Cx</td>
<td>14/42 (33)</td>
<td>65/269 (24)</td>
</tr>
<tr>
<td>Vessel stenosis severity (&gt;50% stenosis) (n) (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>13 (76±18)</td>
<td>84 (81±17)</td>
</tr>
<tr>
<td>RCA</td>
<td>15 (89±15)</td>
<td>120 (86±17)</td>
</tr>
<tr>
<td>Cx</td>
<td>14 (84±14)</td>
<td>65 (75±17)</td>
</tr>
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</table>

LAD, left anterior descending coronary artery; RCA, right coronary artery; Cx, circumflex coronary artery.
Figure 1. Bar graphs of quantitative single-photon emission computed tomography perfusion defect size (PDS) in overall patient population with significant coronary artery disease (n=219) and in those with (group 1, n=30) and without (group 2, n=189) chest pain. LV, left ventricle; striped bars, all patients; dotted bars, patients with myocardial infarction; solid bars, patients without myocardial infarction. (See text for details).

Quantitative SPECT: Assessment of Perfusion Defect Size

Quantitative ⁹⁹mTc SPECT identified most (190 of 219, or 87%) of the patients with significant coronary artery disease while maintaining a high specificity (64 of 73, or 88%). Sensitivity was not significantly different in medicated compared with nonmedicated patients (87%). The prevalence of an abnormal scan was similar (p=NS) in group 1 (28 of 30, or 93%) and group 2 (162 of 189, or 86%) patients.

The perfusion defect size assessed by quantitative SPECT was 20.5±15.0% for all patients with significant coronary disease (n=219) and was not significantly different between groups 1 and 2 (20.9±15.9% versus 20.5±15.6%, respectively) (Figure 1). The perfusion defect sizes were also comparable in medicated and nonmedicated patients in the overall population (20.8±18.9% versus 18.9±15.9%, p=NS) and for those in group 1 (21.8±14.7% versus 18.0±20.6%, p=NS) and group 2 (20.7±15.5% versus 19.7±16.0%, p=NS), respectively (Table 4). Although patients with prior infarction had a larger defect size than those without infarction (27.9±13% versus 15.5±15.5%, p=0.0001), this did not differ significantly between group 1 and 2 patients without infarction (18.1±18.3% versus 15.1±15.0%, p=NS). Likewise, the mean perfusion defect size in the patients without prior infarction who had an abnormal tomogram (≥3% defect) was virtually identical for the two groups (19.4±18.5% versus 19.5±14.5%).

The quantitative polar maps of two representative patients with stenoses of the proximal left anterior descending coronary artery (Figure 2) show similar perfusion defect sizes in symptomatic and asymptomatic patients during exercise.

Presence of Scintigraphic Ischemia

Forty-four percent (118 of 219) of all patients had a reversible perfusion defect by scintigraphy. The frequency of these defects was similar in medicated (53%) and nonmedicated (56%) patients. Although reversible exercise defects occurred more frequently in group 1 (20 of 30, or 67%) than in group 2 (98 of 189, or 52%) patients, the difference was not statistically significant. Similar observations were noted in medicated and nonmedicated group 1 and group 2 patients (Table 4). Furthermore, reversible perfusion defects were fivefold more common in asymptomatic than in symptomatic patients (83% versus 17%, respectively; p=0.0001).

The frequencies of scintigraphic reversibility in the distribution of the left anterior descending and right coronary arteries were similar (p=NS) in group 1 (30% and 30%) and group 2 (22% and 31%) patients, respectively, whereas reversible defects in the circumflex vascular territory were more frequent in group 1 patients (Figure 3).

Categorization of All Vascular Regions by SPECT

In the 219 patients with significant coronary stenoses, 90 vascular territories in 30 group 1 patients and 567 vascular territories in 189 group 2 patients were analyzed (Figure 4). Most of the vascular regions in groups 1 and 2 were normal (58% versus 61%, respectively; p=NS). However, no significant differences were observed in the presence of reversible or nonreversible exercise defects in the vascular territories of group 1 (29% and 13%) and group 2 (21% and 18%) patients, respectively. Similar results were noted in the two groups regardless of whether they were receiving cardiac medications (Table 4).

Analysis was further restricted to patients without prior myocardial infarction, which included 13 in

Table 4. Scintigraphic and Electrocardiographic Results in Medicated and Nonmedicated Patients

<table>
<thead>
<tr>
<th></th>
<th>Medications</th>
<th>No medications</th>
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<tbody>
<tr>
<td></td>
<td>Group 1 (n=23)</td>
<td>Group 2 (n=141)</td>
</tr>
<tr>
<td>Perfusion defect size (% LV)</td>
<td>21.8±14.7</td>
<td>20.7±15.5</td>
</tr>
<tr>
<td>Ischemia (SPECT) (n) (% patients)</td>
<td>14/23 (61)</td>
<td>73/141 (52)*</td>
</tr>
<tr>
<td>Ischemia (ECG) (n) (% patients)</td>
<td>15/23 (65)</td>
<td>47/141 (33)</td>
</tr>
<tr>
<td>Vascular territories by SPECT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (n) (%)</td>
<td>41/69 (59)</td>
<td>259/423 (61)</td>
</tr>
<tr>
<td>Ischemia (n) (%)</td>
<td>18/69 (26)</td>
<td>84/423 (20)</td>
</tr>
<tr>
<td>Scar (n) (%)</td>
<td>10/69 (15)</td>
<td>80/423 (19)</td>
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LV, left ventricle; SPECT, single-photon emission computed tomography; ECG, electrocardiogram.

*p<0.01 vs. ischemia (ECG).
Figure 2. Quantified polar maps in representative patients with (top panel) and without (bottom panel) chest pain during exercise single-photon emission computed tomography. Quantified perfusion defects, involving vascular territories of left anterior descending coronary artery (LAD) in both patients, were comparable at 38% (top) and 41% (bottom). Neither patient had previous myocardial infarction, so exercise perfusion defect size represents area of jeopardized myocardium. Red and black regions indicate normally and abnormally perfused myocardium, respectively. LCX, left circumflex artery; RCA, right coronary artery.
group 1 and 73 in group 2. In these 86 patients, 79% of the abnormal vascular regions had scintigraphic reversibility, whereas 21% did not. Although 63% of the vascular regions with reversible defects were perfused by vessels with 70% or more stenosis, only 7% of the nonreversible regions were perfused by arteries with less than 70% stenosis (p=0.0002). There was, however, no significant difference in the distribution of defect reversibility in the groups.

Electrocardiographic Results—Comparison to SPECT

Stress electrocardiography detected ischemia in 40% (88 of 219) of the patients with coronary artery disease compared with the 54% (118 of 219) prevalence observed with SPECT (p=0.0004). The sensitivity of the stress electrocardiogram improved only minimally (46%) when analysis was restricted to coronary patients without prior infarction. The combination of rest (diagnostic Q waves) or stress (ischemic exercise response) abnormalities improved the sensitivity of the electrocardiogram to 65% (142 of 219), which was still significantly less than the 87% (190 of 219) sensitivity achieved with SPECT (p=0.0001).

Significantly more group 1 than group 2 patients had an ischemic electrocardiographic response to exercise (73% versus 35%, p=0.0001), which was also true for medicated (65% versus 33%, p=0.003) and nonmedicated (100% versus 40%, p=0.003) patients, respectively (Table 4). Although the prevalence of electrocardiographic ischemia (73%) and scintigraphic reversibility (67%) was comparable in symptomatic patients, SPECT was superior to electrocardiography for detecting ischemia in the asymptomatic group (52% versus 35%, respectively; p=0.01). Notably, of the 88 patients with ischemia by electrocardiographic criteria, only 22 (25%) had accompanying chest pain during exercise, whereas the majority (75%) had silent ischemia.

**Tomographic Perfusion Defect Size Versus Ischemia Severity by Electrocardiography**

No correlation was found between the scintigraphic perfusion defect size and the electrocardiographic ischemia score in all patients with coronary stenosis (r=0.04) or in those without prior myocardial infarction (r=0.18). The correlation remained poor when analysis was restricted to group 1 (r=0.22) or group 2 (r=0.07) patients. Separate analysis of individual electrocardiographic severity variables (e.g., maximal ST segment depression, number of abnormal leads, and time to first ST change) also demonstrated poor and statistically nonsignificant correlations to scintigraphic perfusion defect size.

**Discussion**

The major conclusion of this study is that coronary artery disease patients without chest pain during exercise testing have a similar extent of abnormally perfused myocardium when compared with those with chest pain as assessed by quantitative ²⁰¹Tl tomography. The patient population studied was unique in that they were evaluated early in the natural history of their coronary artery disease. Most patients had only one-vessel involvement and no prior history of myocardial infarction. Patients with previous coronary revascularization procedures were excluded. The results of this study emphasize that silent myocardial ischemia is extremely common in a low-risk population with coronary artery disease. With the use of quantitative SPECT, we have demonstrated that asymptomatic and symptomatic perfusion defects represent a comparable extent of jeopardized myocardium and are thus likely to be of similar prognostic importance.

The lack of chest pain during exercise testing did not indicate a lesser extent of abnormal myocardial perfusion in the present study. The frequency of abnormal tomographic scans and the extent and prevalence of reversible perfusion defects were comparable among patients with and without chest pain during exercise testing. Similar results were also found in the subgroup of patients without prior

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**Figure 3.** Bar graphs of scintigraphic evidence of ischemia by vessel in patients (Pts) with (group 1) and without (group 2) exertional chest pain. Although percentage of patients with ischemia in vascular territories of left anterior descending (LAD) and right (RCA) coronary arteries were comparable in both groups, more group 1 than group 2 patients had ischemia in circumflex (Cx) vascular territory.

**Figure 4.** Bar graphs of scintigraphic categorization of all vascular regions in 30 group 1 and 189 group 2 patients. Most vascular territories in both groups were normal. Likewise, no significant differences were observed for percent of regions with scar and ischemia in the two groups.
infarction in whom any observed perfusion defect should presumably reflect only viable myocardium.

Of note, reversible defects in the circumflex vascular territory were more prevalent in patients with than in those without chest pain (27% versus 11%, \( p=0.04 \)), respectively. However, the severity of stenosis and the presence of concomitant multivessel disease were similar in patients with circumflex, right, or left anterior descending coronary artery stenoses. Why patients with circumflex disease were more likely to develop chest pain during exercise testing is unexplained but has also been reported by other investigators.\(^{19}\)

In the present study, late (24-hour) imaging was not performed. Although a late image may have yielded additional patients with redistribution, this was not part of the study protocol. There is no a priori reason to assume that such late redistribution would occur with a different frequency in symptomatic and asymptomatic patients.

Previous Holter studies have demonstrated that asymptomatic ischemic episodes exceed symptomatic episodes by threefold to fourfold in selected patients with documented coronary artery disease.\(^{1-3}\) Studies examining the presence of silent ischemia by Holter recordings in high-risk patients with unstable angina\(^{11}\) and in those after myocardial infarction\(^{12}\) document an increased cardiac event rate when silent ischemia is present. Our scintigraphic data are consistent with these Holter studies in that silent reversible perfusion defects were more prevalent than symptomatic ones. It is likely that silent exercise-induced perfusion defects that undergo redistribution represent true ischemia in many of our patients. However, there is no direct evidence to support this contention. The early detection of possible silent ischemia by exercise SPECT may identify a patient group at increased risk for cardiac events among an otherwise relatively low-risk coronary disease population.

Coronary Anatomy in Patients With and Without Chest Pain

The anatomical extent and severity of coronary artery disease were found to be similar in patients with and without chest pain, which is consistent with previous reports.\(^{18,19,27,28}\) This study emphasizes that exercise-induced chest pain is a nonspecific and insensitive finding in a patient population primarily with one-vessel disease. In our population, only 14% of patients with significant coronary artery stenosis had chest pain during exercise, whereas 20% of patients with insignificant stenosis and 12% of patients with normal coronary arteries had exercise-induced chest pain. In patients similar to the present study population, chest pain would be a poor end point for evaluating anti-ischemic therapy and in fact was misleading.

Tomographic Perfusion Defect Size and Electrocardiographic Ischemia

The overall sensitivity for detecting coronary artery disease was significantly higher with scintigraphy than with electrocardiography (87% versus 65%, \( p=0.0001 \)). Furthermore, SPECT was superior to the stress electrocardiogram for detecting functionally significant coronary artery stenosis in the asymptomatic group (52% versus 35%, respectively; \( p=0.01 \)), although there was a poor correlation \(( r=0.04)\) between scintigraphic perfusion defect size and the severity of electrocardiographic ischemia. We have previously shown that perfusion defect size quantified by tomography significantly increases with anatomical severity\(^ {29}\) and extent\(^ {26}\) of coronary artery disease, particularly when the left anterior descending coronary artery is stenosed proximally.\(^ {29}\) The present data suggest that quantitative tomography is a more precise method than exercise electrocardiography for the early identification of patients with coronary stenosis and for estimation of the extent of abnormal myocardial perfusion in asymptomatic patients. This is not surprising since electrocardiographic ST segment changes as well as angina are recognized as relatively late manifestations of acute myocardial ischemia.\(^ {30-32}\)

Previous Studies Attempting to Quantify Silent Ischemia

Few studies with myocardial scintigraphy have attempted to quantify differences in the extent of perfusion defects between symptomatic and asymptomatic patients.\(^ {18,19,33}\) Hecht et al\(^ {19}\) reported their observations with \(^ {201}\)TI SPECT and observed a similar number of reversible tomographic segments during exercise imaging in a retrospective analysis of patients with and without chest pain. In contrast to the present report, Hecht et al studied only patients with reversible perfusion defects, the majority of whom had a history of angina and multivessel coronary disease. Thus, most of these patients were evaluated late and had extensive coronary disease, previous infarction, or both. By selecting only patients with a reversible defect, Hecht et al may have decreased their likelihood of finding a scintigraphic difference between symptomatic and asymptomatic patients, even if one was present. Furthermore, their tomographic analysis was restricted to three slices rather than the entire myocardium and thus was semiquantitative. In a recent small retrospective study by Kahn et al,\(^ {18}\) patients had a similar extent of exercise-induced myocardial ischemia, regardless of chest pain symptoms, as assessed by tomographic imaging with iodine-123 phenylpentadecanoic acid—a metabolic and perfusion agent. Their study design had the same limitations as the report of Hecht et al.

Cohn et al\(^ {33}\) studied 40 coronary artery disease patients with \((n=24)\) and without \((n=16)\) chest pain using gated radionuclide angiography to determine differences in the severity and extent of change in global and regional ejection fractions between these two patient groups. A similar depression in global and regional left ventricular ejection fractions suggested a similar extent of ischemic myocardium in both the
symptomatic and asymptomatic patients. Ejection fraction, however, is markedly dependent on preload, afterload, and heart rate, and no data were reported as to whether exercise heart rate, blood pressure, or cardiac volumes were also similar in the two groups.

**Thallium Redistribution and Myocardial Ischemia**

In the present study, we evaluated perfusion defects during exercise that underwent partial or total redistribution at rest. Although a transient perfusion defect does not necessarily indicate a true decrease in myocardial blood flow during exercise, it does clearly signify relative myocardial hypoperfusion (i.e., heterogenous perfusion), which often indicates ischemia.

Furthermore, there is compelling evidence that heterogeneous regional myocardial perfusion during exercise usually leads to additional manifestations of ischemia (i.e., global and regional left ventricular dysfunction) since myocardial segments with transient perfusion defects during SPECT also develop regional wall motion abnormalities by echocardiography. To a certain extent, transient regional wall motion abnormalities have also been observed after pharmacological vasodilation with dipyridamole and adenosine, the latter associated with transient SPECT perfusion defects and implying coronary steal–induced ischemia.

**Potential Role of Perfusion Defect Size for Evaluating Prognosis**

The scintographic results of the present study support the claims of previous investigators that the presence of symptomatic or asymptomatic myocardial ischemia during exercise identifies patients at similar high risk for cardiac events. Furthermore, pharmacological vasodilation with dipyridamole and adenosine can produce transient myocardial perfusion defects, which are also associated with future ischemic events in patients with chronic stable coronary artery disease and in those after myocardial infarction. Our data suggest an anatomical and physiological substrate underlying this similar high event rate, namely, a similar severity and extent of coronary artery disease as well as a comparable extent of abnormal myocardial perfusion in symptomatic compared with asymptomatic patients. Natural history and intervention trials indicate that an inordinately high mortality rate is seen in stable patients with three-vessel coronary artery disease who have exercise-induced ischemia and that mortality can be significantly reduced in this population by coronary revascularization. This is presumably due to the larger amount of myocardium at risk for subsequent ischemic events in patients with multivessel compared with one-vessel coronary disease. With the use of SPECT, the extent of myocardium at risk can now be accurately quantified, which may be clinically and prognostically useful in patient management. The presence of chest pain appears relatively less important in this respect. The observations made in our trial of stable patients do not lessen the importance of eliciting a history of recent exacerbation or changing patterns of angina.

The presence of chest pain and the anatomical extent or severity of coronary artery disease alone lack precision in identifying the amount of jeopardized myocardium, underscoring an important adjunctive role of quantitative tomographic perfusion imaging. Further investigation should focus on whether the quantified perfusion defect size can more precisely stratify risk in patients with coronary artery disease and whether reduction of defect size, by either pharmacological or invasive intervention, can improve prognosis.

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Quantitative Tomography for Assessment of Silent Ischemia

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