Detection of Residual Jeopardized Myocardium
3 Weeks After Myocardial Infarction
by Exercise Testing with Thallium-201
Myocardial Scintigraphy

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SUMMARY The usefulness of thallium-201 (TI-201) exercise myocardial scintigraphy in identifying patients with multivessel coronary artery disease (MVCA) and residual jeopardized myocardium after myocardial infarction (MI) was evaluated in 32 patients 3 weeks after MI. All patients underwent 1) limited multilead submaximal treadmill testing, 2) thallium-201 (TI) myocardial scintigraphy at end-exercise and at rest, and 3) coronary and left ventricular angiography.

TI-201 perfusion defects were categorized as either reversible (ischemia) or irreversible (scar). The conventional exercise test was designated positive if there was ST depression ≥ 1 mm and/or angina. Jeopardized myocardium (JEP) was defined angiographically as a segment of myocardium with normal or hypokinetic wall motion supplied by a significantly stenotic major coronary artery. MVCA was defined as two or more significantly stenotic coronary arteries. "Significant" coronary stenosis was categorized as either 50–69% diameter narrowing or ≥ 70% diameter narrowing, thereby yielding, respectively, two subgroups each of jeopardized myocardium (JEP-50 and JEP-70) and MVCA (MV-50 and MV-70).

Clinical findings of angina, heart failure or ventricular arrhythmias during the late convalescent period after MI occurred in four of 10 patients (40%) with MV-50, five of 16 (31%) with MV-70, four of 10 (40%) with JEP-50, and five of 18 (28%) with JEP-70, and thus were insensitive for detecting MVCA and JEP.

Reversible ischemia and/or a positive conventional exercise test occurred in five of 10 patients (50%) with MV-50, 13 of 16 (81%) with MV-70, four of 10 (40%) with JEP-50 and 15 of 18 (83%) with JEP-70. All eight patients with both TI-201 reversible ischemia and a positive conventional exercise test had JEP-70. In 30 of 31 patients (97%) with angiographic asynergy, TI-201 scar was detected. No complications were associated with exercise testing.

Thus, 3 weeks after MI, TI-201 exercise myocardial scintigraphy is a safe, useful, noninvasive tool for identifying patients with MVCA and residual JEP and is much more reliable than clinical findings during convalescence after MI.

BECAUSE CORONARY ANGIOGRAPHY is not recommended in all survivors of myocardial infarction,1 noninvasive identification of patients with multivessel coronary artery disease (MVCA) or residual ischemic myocardium after myocardial infarction (MI) is important to guide therapy and estimate prognosis. Limited submaximal exercise testing soon after MI provides objective information concerning the capacity for physical exercise,2 detects arrhythmias that may be prognostically important,3-4 and may be useful in assessing the coronary anatomy.5 Myocardial perfusion imaging with thallium-201 (TI-201) has been shown to be a useful, noninvasive method for detecting prior MI6 and stress-induced regional myocardial ischemia.7

The purpose of this study was to assess the value of conventional submaximal exercise testing combined with TI-201 myocardial scintigraphy in detecting MVCA and residual jeopardized myocardium (JEP) in patients before hospital discharge, 2-3 weeks after MI.

Methods

Admission Criteria

The study population consisted of a group of patients admitted consecutively to our coronary care unit who satisfied all of the following criteria: 1) acute MI, diagnosed by typical rise and fall of the CK-MB isoenzyme in the appropriate clinical setting; 2) willingness to undergo submaximal exercise testing, TI-201 myocardial scintigraphy and coronary and left ventricular angiography; and 3) absence, 2 weeks after MI, of unstable angina, severe (New York Heart Association [NYHA] class IV) heart failure, serious ventricular arrhythmias at rest, second- or third-
degree atroventricular block, limiting musculo-skeletal abnormalities, valvular heart disease, blood pressure exceeding 180/105 mm Hg and any other debilitating medical problem. Complications during the acute phase of MI that had resolved by 2 weeks after infarction did not preclude admission to the study.

Clinical Data

The clinical convalescence of the survivors of acute MI was classified as either complicated or uncomplicated. The complicated group had one or more of the following: 1) angina pectoris more than 5 days after infarction, 2) serious ventricular arrhythmias, defined as more than five premature ventricular contractions (PVCs) per minute, multifocal, R-on-T, two or more in sequence, or ventricular fibrillation more than 5 days after infarction, and 3) congestive heart failure (CHF), defined as a persistent S₃ gallop and basilar rales or chest x-ray evidence of pulmonary edema more than 10 days after infarction. CHF and ventricular arrhythmias occurring earlier in the postinfarction period did not qualify the patient as having a complicated convalescence. All patients were evaluated clinically by at least two staff cardiologists daily, and spent at least 4 days in the coronary care unit. Progressive mobilization and ambulation for 1–3 weeks after the intensive care phase was performed on a general medical ward adjacent to the coronary care unit, and rhythm-monitoring facilities were available.

Exercise Testing

Exercise testing⁸ was performed 2½–3 weeks after infarction on a motor-driven treadmill 2 or more hours postprandially. Each patient was interviewed and examined by a physician and informed consent was obtained. Twelve-lead ECGs were recorded at rest and at the end of each stage of exercise and at 2, 4 and 6 minutes after exercise. A three-channel oscilloscope displaying leads V₁ to V₄ was continuously monitored. Blood pressure was recorded at rest, every 3 minutes beginning 2 minutes after the onset of exercise, at the end of exercise, and at 2, 4 and 6 minutes after exercise.

Treadmill exercise was conducted in 3-minute uninterrupted stages using the following treadmill settings⁶: stage 0 — speed 1.7 miles per hour (mph) and 0% grade; stage ½ — speed 1.7 mph and 5% grade; stage 1 — speed 1.7 mph and 10% grade; stage 2 — 2.5 mph and 12% grade; stage 3 — speed 3.4 mph and 14% grade; and stage 4 — speed 4.2 mph and 16% grade. All patients started exercise at stage 0. Each patient exercised to 75% of his or her maximum predicted heart rate for age and sex⁶—¹⁸ or until the appearance of any of the following: increasing chest pain compatible with angina pectoris, exaggerated fatigue or dyspnea, claudication, dizziness, blood pressure drop of 10 mm Hg below the peak value at the previous stage, three successive PVCs, signs of cerebral insufficiency, or flat or downsloping ST-segment depression greater than 2 mm; ST-segment elevation alone was not an indication for termination of the test.

The exercise test was interpreted as positive or negative. A test was judged positive when the patient either experienced chest pain compatible with angina pectoris¹⁴—¹⁸ or developed diagnostic ischemic ECG changes, including 1) 1 mm or more of ST-segment depression in any recorded lead 80 msec after the J point during or after exercise in a patient with isoelectric ST segments at rest; 2) additional ST depression of 1 mm or more at 80 msec after the J point in patients with abnormal ST segments at rest;¹³ and 3) 2 mm or more of ST depression at 80 msec after the J point during or after exercise in patients receiving digitalis or with upsloping ST segments during exercise.¹⁴—¹⁶ The exercise test was considered negative if it did not satisfy the criteria for a positive test, regardless of the maximal heart rate achieved.

The CK-MB isoenzyme was assayed before exercise in all patients and again 8 and 24 hours after exercise.

Angiography

All patients underwent selective coronary angiography and biplane cine left ventricular angiography 3 weeks after MI. Coronary angiograms were reviewed by at least one experienced angiographer and a cardiac radiologist using multiple projections. The maximal luminal diameter stenosis for each major coronary artery was estimated visually and determined by consensus. In cases of disagreement, the stenotic area was compared with the normal-appearing vessel by means of calipers. Obstructions of large diagonal or marginal branches were considered as lesions of the left anterior descending or circumflex coronary arteries, respectively. There were no complications resulting from angiography.

End-diastolic and end-systolic left ventricular silhouettes in anteroposterior and lateral projections were superimposed using fixed external x-ray markers as references. Regions of akinesis and dyskinesia (abnormally contracting segments¹⁷) were thus objectively identified.

JEP (fig. 1) was defined angiographically as a hypokinetic or normally contracting zone of myocardium supplied by a stenotic major coronary vessel. If the vessel's maximal luminal stenosis was 50–69%, the patient was designated JEP-50; if the vessel's maximal stenosis was ≥ 70%, the patient was designated JEP-70.

Nonjeopardized myocardium (non-JEP) was defined as myocardium with normal or hypokinetic wall motion supplied by a vessel having no stenosis ≥ 50%. Akinetie or dyskinetic segments were assumed to represent scar and were thus considered non-JEP.

MV-70 was defined as two or more major coronary vessels with ≥ 70% stenoses (MV-70). Patients with two or more major coronary vessels with ≥ 50% stenoses but < 70% (i.e., not MV-70) were classified as MV-50. Single-vessel coronary artery disease (SVCAD) was defined as one major vessel with ≥ 50% stenosis but without other major vessels having ≥ 50% stenoses.
Myocardial Scintigraphy

TL-201 (thallous chloride) was administered intravenously in a dose of 1.5 mCi (New England Nuclear Corp., North Billerica, Massachusetts) as the patient approached signs or symptoms limiting end-exercise. Exercise was maintained for 30–60 seconds after radionuclide injection if chest pain, ECG changes and blood pressure were stable.

With the patient supine, postexercise myocardial images were recorded sequentially in the 45° left anterior oblique, anterior and left lateral positions beginning within 3–5 minutes after tracer administration. Rest (reequilibration) myocardial scintigrams were obtained in the same positions 4 hours after exercise. Imaging in each view required approximately 5 minutes to acquire 400,000 counts per image on a 37-

Figure 1. Definition of jeopardized myocardium (JEP). End-diastolic and end-systolic left ventricular contrast angiographic silhouettes were superimposed using fixed x-ray markers (large dots) as references in the anteroposterior (AP) and lateral projections. Silhouettes were divided into zones of regional coronary perfusion as shown (LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery). In the examples shown, there is generalized akinesis in the LAD zone of distribution. If the RCA and LCX were significantly narrowed, this patient would be classified as having jeopardized myocardium; otherwise the patient would be classified as "nonjeopardized," because the residual normally contracting myocardium would be supplied by patent coronary vessels.

Figure 2. Example of thallium-201 exercise scintigraphy in a study patient. On the left is an immediate postexercise thallium-201 myocardial image and on the right a delayed image, both in the 45° left anterior oblique position. Computer processing displays regions of maximal thallium-201 uptake as white and red, respectively. On the left, perfusion defects are present in both the septal and inferior regions immediately after exercise. On the right, 4 hours after exercise, there is significant thallium-201 uptake in the septal region and a persistent defect in the inferior region. The conventional exercise test was negative. Angiographically, the patient had 70% stenosis of the left anterior descending artery, 100% stenosis of the right coronary artery and inferior wall akinesis. Thus, the jeopardized myocardium in the zone of distribution of the left anterior descending coronary artery was detected only by thallium-201 scintigraphy.
1. TABLE

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<th>Pt</th>
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<td>U</td>
<td>Ant akinesis; inf hypokinesis</td>
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*Non-dominant.

Abbreviations: U = uncomplicated; C = complicated; MI = myocardial infarction; inf = inferior; post = posterior; ant = anterior; lat = lateral; CAD = coronary artery disease; LM = left main; LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery; MV-50 and MV-70 = multivessel coronary artery disease of 50-69% and ≥ 70% stenosis, respectively; JEP-50 and JEP-70 = myocardium jeopardized by 50-69% and ≥ 70% stenosis, respectively.

(or their combinations) using all three views.* Diminished activity seen at the apex in one view or only in the left lateral position was not considered significant. A defect present during exercise and at rest was considered scar, while a defect present only during exercise was considered reversible ischemia. Either partial or complete resolution of a defect qualified as reversible ischemia. Further, the reversible defect could occur either adjacent to the zone of infarct or widely separated from it.

Statistics

To detect patients with MVCA or JEP, sensitivity was defined as the ratio of the true positives to the sum of true positives and false negatives. Specificity was the ratio of true negatives to the sum of true negatives and false positives. Predictive value was the ratio of true positives to the sum of true positives and false positives.

Continuous data are reported as mean ± SEM. The t test was used to assess differences between means of independent observations, the chi-square test to assess differences between proportions.

Results

Clinical Data

Twenty-seven males and five females (mean age 50 ± 2 years) with definite MI admitted between
December 1977 and September 1978 fulfilled the study criteria (table 1). Ten patients with acute MI were excluded because of severe angina, heart failure, valvular disease, limiting musculoskeletal abnormality or other debilitating medical illness. One additional patient refused angiography. No patient satisfying the criteria for admission to the study refused exercise testing with TI-201 scintigraphy.

Electrocardiographic localization of infarction was anterior in 16 patients, inferior in 11 and indeterminate in five. Six patients had remote antecedent MI. Twenty patients had transmural and 12 had nontransmural MI.

Convalescence after MI was complicated in 10 patients: four had CHF, three had angina pectoris and three had combinations of ventricular arrhythmias, CHF and angina pectoris. Seven of the 10 patients with a complicated convalescence also had ventricular arrhythmias or CHF during the acute phase of their hospitalization. The remaining 22 patients had an uncomplicated convalescence, although eight of these had had early CHF or ventricular arrhythmias.

### Angiography

Six of the 32 patients (19%) had SVGAD, 10 (31%) had MV-50 CAD, and 16 (50%) had MV-70 CAD. Four of the 32 patients (13%) had non-JEP myocardium, 10 (31%) had JEP-50 and 18 (56%) had JEP-70.

Twenty-five patients had areas of akinesis or dyskinesis; 11 had areas of hypokinesis (five had both akinesis/dyskinesis and hypokinesis in different areas). One patient had normal left ventricular contraction.

### Clinical Convalescence

Four of the 10 patients (40%) with MV-50 CAD and
five of the 16 (31%) with MV-70 CAD had a complicated convalescence. Similarly, four of the 10 patients (40%) with JEP-50 and five of the 18 (28%) with JEP-70 had a complicated convalescence. There was no relation between the occurrence of early ventricular arrhythmias or heart failure (15 patients) and the presence of residual JEP or MVCAD. Thus, clinical criteria were relatively insensitive for detecting JEP or MVCAD.

Exercise Testing with TI-201 Scintigraphy

Of the 32 study patients, 14 had a positive conventional exercise test and 13 patients had reversible ischemia by TI-201 scintigraphy (fig. 2 and table 1). Eight patients had both a positive exercise test and a reversible thallium defect. Nineteen patients had either a positive exercise test or reversible ischemia by TI-201 scintigraphy. All but three patients attained at least 60% of their maximum predicted heart rate for age and sex. Patients who had a positive exercise test or a reversible TI-201 defect attained 67 ± 2% of their maximum predicted heart rate, with a mean treadmill time of 526 ± 48 seconds, and attained a mean work load of 6.16 ± 0.57 equivalents of resting energy expenditure (METs). Patients who had a negative exercise test and no reversible TI-201 defect attained 73 ± 2% maximum predicted heart rate, with a mean treadmill time of 452 ± 58 seconds, and attained a mean work load of 5.19 ± 0.71 METs. The percent maximum predicted heart rate, treadmill time and work load in METs were not significantly different between the two groups. There were no complications associated with exercise testing, and CK-MB isoenzyme did not become elevated after exercise.

Twenty-five of the 32 patients were receiving cardiac medications at the time of exercise testing: nitrates — 22 patients; propranolol — nine patients; quinidine — three patients; digoxin — one patient. The one patient receiving digoxin at the time of exercise testing had both a positive exercise test and reversible ischemia by TI-201 scintigraphy. Twelve of the 22 patients taking nitrates, six of the nine patients taking propranolol and four of seven patients taking neither medication had either a positive exercise test or reversible ischemia by TI-201 scintigraphy.

Detection of MVCAD

The ability of thallium-201 exercise scintigraphy and the submaximal exercise test to detect MVCAD was evaluated (fig. 3). Of the 10 patients with MV-50 CAD, four (40%) had a positive conventional exercise test and two (20%) had a reversible TI-201 defect. Half of the patients with MV-50 CAD had either a positive conventional exercise test or a reversible TI-201 defect or both. One of the six patients with SVCAD (17%) had both a positive exercise test and a TI-201 defect.

Nine of the 16 patients (56%) with MV-70 CAD had a positive conventional exercise test, and 10 (63%) had a reversible TI-201 defect. Thirteen of these 16 patients with MV-70 CAD (81%) had either a positive exercise test or a reversible TI-201 defect or both. Six of the 16 patients (38%) without MV-70 CAD had either a positive exercise test or a reversible TI-201 defect or both, but five of these patients had MV-50 CAD.

Thus, the combination of exercise testing and TI-201 scintigraphy yields a sensitivity of 81% for detection of MV-70 CAD. The specificity for detecting MV-70 CAD is only 62%, but five of the six false positives were MV-50. The remaining false positive had SVCAD but, as explained below, this patient had JEP.

Detection of JEP

The results of TI-201 exercise scintigraphy and submaximal exercise testing were also analyzed with respect to the detection of JEP (fig. 4). Three of 10 patients (30%) with JEP-50 and none of four with non-JEP had a positive conventional exercise test. Similarly one of nine (11%) with JEP-50 and none of four with non-JEP had a reversible TI-201 defect. Either a positive exercise test or a reversible TI-201

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defect or both were found in four of 10 patients (40%) with JEP-50 but in none of the four patients with non-JEP.

Eleven of 18 patients (61%) with JEP-70 and three of 14 (21%) without JEP-70 had a positive conventional exercise test. Twelve of 18 (67%) with JEP-70 had a reversible Tl-201 defect, while 15 of 18 (83%) with JEP-70 had either a positive conventional exercise test or a reversible Tl-201 defect or both.

Thus, the sensitivity of exercise testing combined with scintigraphy was 83% for detecting JEP-70. The specificity for detecting patients with JEP was 100%. Thus, the predictive value of a positive exercise test or reversible Tl-201 defect for detecting JEP was 100%.

However, the number of patients with non-JEP in this series was small, possibly limiting the usefulness of specificity and predictive value. The specificity for detecting JEP-70 was 78% with combined testing; all four patients falsely detected were actually JEP-50.

The predictive value of any positive response (either a positive conventional exercise test or a reversible Tl-201 defect or both) for detecting JEP-70 was 79%. All eight patients who had both a positive exercise test and a reversible Tl-201 defect were JEP-70. Thus, the predictive value for the combined positive response for detecting JEP-70 was 100%.

**Scar Detection**

Thirty-one of 32 patients had angiographic asynchrony on left ventriculography. In 30 of these 31 patients (97%), a scar corresponding to areas of asynchrony on left ventriculography was detected by Tl-201 scintigraphy. Of the remaining two patients, left ventriculography showed inferior hypokinesis in one and normal contraction in the other. Thus, Tl-201 scintigraphy was highly sensitive (97%) for the detection and localization of myocardial scar.

**Discussion**

This study demonstrates the usefulness of Tl-201 exercise scintigraphy in the detection of JEP and MVCAD in patients three weeks after MI.

**Clinical Criteria**

The prevalence of MVCAD or JEP in this study was high and may not necessarily represent their prevalence in all survivors of MI. Several studies, however, have indicated a high prevalence of MVCAD in asymptomatic survivors of acute MI. Although older age, angina after MI and prior MI are associated with increased prevalence of MVCAD, the presence of complications in the postinfarction convalescence has not been predictive of MVCAD. Similarly, in this study, clinical criteria were not sensitive indicators for MVCAD or for JEP.

**Exercise Testing with Tl-201 Scintigraphy**

In patients with equivocal exercise stress tests due to conduction abnormalities, left ventricular hypertrophy and resting ST-segment depression, Tl-201 exercise scintigraphy identifies abnormal myocardial perfusion, stress-induced ischemia and thus, indirectly, significant coronary arterial lesions. Low-level exercise testing soon after MI has been recommended by some investigators to determine physical work capacity, to detect arrhythmias and to predict extensive coronary artery disease.

The present study used low-level exercise testing and Tl-201 exercise scintigraphy to detect MVCAD and JEP. A substantial percentage of patients with significant coronary disease was identified, despite the potential limitations in obtaining a satisfactory exercise test or Tl-201 myocardial image secondary to restricted heart rate, medications, ST abnormalities at rest, left ventricular dysfunction and myocardial scar.

In this study, exercise scintigraphy identified a group of patients with Tl-201 defects but with negative conventional exercise tests, thus increasing the sensitivity of exercise testing for detecting JEP and MVCAD. In all patients with reversible Tl-201 defects, these defects corresponded to areas of normal or hypokinetic wall motion by left ventriculography supplied by significant coronary stenotic lesions. However, these defects did not always predict the areas of maximum coronary stenosis.

In this study our standard for comparison is based on the angiographic coronary anatomy and left ventricular function. Tl-201 exercise scintigraphy may well be superior for assessing the physiologic significance of coronary artery lesions. Further studies are needed to estimate the prognosis of patients with abnormal responses during exercise scintigraphy. Theoretically, these patients are at high risk of developing future coronary events — recurrent MI, ventricular arrhythmias and death.

**Detection of MVCAD**

The combination of exercise testing and Tl-201 scintigraphy in our study was sensitive (81%) for MVCAD defined by stenoses ≥ 70%. The specificity of 84% for all MVCAD is limited by the small number of patients (n = 6) with SVCAD. There was a relatively low specificity (59%) for MV-70 patients. However, of the six patients without MV-70 who had positive tests, five were MV-50 and one was JEP-70. The predictive value of a positive exercise test or reversible Tl-201 defect was thus 95% for all MVCAD. Inability to detect MVCAD with Tl-201 scintigraphy may have been due to low-level exercise or the absence of differential flow to stenotic areas. Further, the ability of Tl-201 scintigraphy to detect areas of reversible ischemia depends in part on the location of the ischemic area, and may be difficult in the presence of nearby scar.

**Detection of JEP**

The prognosis of patients with coronary artery disease is generally considered a function of the number of diseased coronary vessels. However, in the postinfarction patient, a better descriptor of
propensity toward recurrent angina or MI might be whether the diseased coronary vessels are supplying viable myocardium or scar. Viable myocardium supplied by diseased coronary vessels would be "jeopardized," scar, of course, would represent the sequelae of prior MI and would therefore no longer be jeopardized.

Limitations exist in the clinical determination of viable and nonviable myocardium. In this study we have chosen to accept angiographic evidence of normal wall motion or hypokinesis as an indication of viable myocardium and akinesis or dyskinesis as indicative of nonviable myocardium. In some instances, ischemic but viable tissue might exhibit akinesis or dyskinesis angiographically, leading to underestimation of the extent of jeopardized tissue by our method.

In the present study, 19 of 28 patients with JEP (68%) (both groups) were detected by TI-201 stress scintigraphy and conventional exercise testing (sensitivity = 68%). When stenosis ≥ 70% was the criterion, 15 of 18 patients with JEP (83%) were identified (sensitivity = 83%). The lower sensitivity than reported in previous studies would be expected in view of the heart rate limitation (75% of maximum predicted for age and sex). Despite the limitations, a substantial percentage of patients with JEP-70 was identified, and the predictive value of a positive response for all JEP (> 50% stenosis) was 100% 3 weeks after infarction in this study.

**Scar Detection**

Location of the myocardial scar using TI-201 scintigraphy has been shown. This study verifies those findings. In the patient with SV CAD and normal left ventricular contraction, no scar was shown. The other patient with no scar by TI-201 scintigraphy had inferior hypokinesis and a 50% stenosis of the right coronary artery by angiography. Thus TI-201 scintigraphy is highly sensitive (97%) in detecting myocardial scar corresponding to areas of left ventricular asynergy by angiography 3 weeks after MI.

**Clinical Implications**

Most patients with MI have CAD. Recent studies have suggested a high prevalence of MVCAD in selected subgroups after MI, in both symptomatic and asymptomatic patients.

Three weeks after MI, TI-201 myocardial scintigraphy increases the sensitivity of submaximal exercise testing in detecting MVCAD and JEP. A reversible perfusion defect on TI-201 scan or a positive submaximal exercise test suggests MVCAD or JEP or both (fig. 5). The presence of both a reversible perfusion defect and a positive submaximal exercise test suggests JEP supplied by a stenosis ≥ 70%. A negative submaximal exercise test and absence of reversible perfusion defect by TI-201 scintigraphy does not rule out MVCAD, although MV-70 and JEP-70 are less likely. TI-201 exercise myocardial scintigraphy may be important in assessing the physiologic and prognostic significance of coronary artery lesions.

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