Thallium-201 Myocardial Scintigraphy in Patients with Triple-Vessel Disease and Ischemic Exercise Stress Tests

JEFFREY LEPPO, M.D., TADA YIPINTSOI, M.D., PH.D., RONALD BLANKSTEIN, M.D., ROBERT BONTEMPES, B.S., LEONARD M. FREEMAN, M.D., LENORE ZOHMAN, M.D., AND JAMES SCHEUER, M.D.

SUMMARY Thirty patients with triple-vessel coronary artery disease proven by angiography, symptomatic angina and a positive ECG stress test were evaluated with thallium-201 (201Tl) scintigraphy. Twenty patients also had aortocoronary saphenous vein bypass surgery; 15 of them had repeat noninvasive evaluation. Seventy percent of these patients showed ischemia by 201Tl scintigraphy, of which one-half returned to normal after surgery. Postoperative reversion of the ECG stress test together with 201Tl stress/reperfusion imaging correlated well with the completeness of surgical revascularization. We could not explain the prevalence (80%) of infarcts detected by 201Tl in this group, of which 76% could be anatomically correlated to epicardial scars. The positivity of infarcts by 201Tl exceeded that predicted by previous history of infarction, Q waves on resting ECG or ventriculographic akinesis. These observations suggest that 201Tl scintigraphy is a useful noninvasive tool in the follow-up and understanding of patients with coronary heart disease. These conclusions also support the concept that 201Tl stress imaging need not have the identical connotation as the ECG stress test.

A NONINVASIVE TEST should be capable of following the progression or regression of disease. Stress thallium-201 (201Tl) myocardial scintigraphy has been reported to detect ischemia in patients with suspected coronary artery disease with a higher sensitivity and specificity than maximal or submaximal ECG stress testing.1-3 In patients with documented coronary artery disease, the high sensitivity of 201Tl scintigraphy should be valuable in assessing medical or surgical therapy.4,6 Bailey et al.5 reported no significant difference in positive ischemic responses by 201Tl (80%) compared with ECG (73%) in triple-vessel coronary artery disease, while Botvinick et al.2 noted a relatively low (44%) sensitivity for ECG and a significantly higher one (87%) for 201Tl. In larger study groups of patients with triple-vessel disease, several authors have reported ischemic ECG responses of greater than 90%.7-9 Regional ischemia with less severe coronary artery disease should provide contrast between underperfused and highly perfused areas. However, in triple-vessel disease ischemia may be diffuse or global and, therefore, areas with markedly different flow patterns may not be present.10,11 This condition might decrease the sensitivity of the scintigram for ischemia. Also, the relatively high incidence of epicardial scar tissue in patients with severe coronary artery disease12,13 may mask the scintigraphic interpretation of ischemia in the adjacent myocardial region.

No previous report has focused specifically on 201Tl scintigraphy in patients with triple-vessel disease. In this study we selected patients who had angiographically proven triple-vessel disease, angina pectoris and positive ECG stress tests so that the sensitivity of 201Tl scintigraphy could be specifically evaluated in this group. The majority of these patients were being considered for aortocoronary bypass surgery, so this patient selection permitted repeat noninvasive evaluation postoperatively. In this study we report the combination of different methods for identifying myocardial ischemia and infarction. We also compare the results of these evaluations before and after coronary bypass surgery.

Methods and Terminology

Angiography

The Judkins technique14 was used for all coronary arteriograms and biplane contrast left ventriculography. The time interval between angiography and 201Tl scintigraphic evaluation was within 3 weeks in 28 patients and 2 and 3 months, respectively, in the two other patients. Left ventricular analysis included end-diastolic pressures and ejection fraction. The ventriculogram wall motion was qualitatively evaluated, and significant stenotic lesions were visually estimated as greater than 70% diameter narrowing of a vessel. The presence or absence of collateral vessels was also noted. Triple-vessel disease was defined as significant proximal stenosis in the three major coronary vessels, or the equivalent lesions in the left anterior descending and circumflex arteries in patients with small, non-dominant right coronary arteries. The angiograms were interpreted by at least two experienced readers who were not involved in the scintigraphic aspects of the study.

From the Department of Cardiology and Nuclear Medicine, Montefiore Hospital and Medical Center and Albert Einstein College of Medicine, Bronx, New York.

Address for reprints: Jeffrey Leppo, M.D., Department of Cardiology, Montefiore Hospital and Medical Center, 111 East 210th Street, Bronx, New York 10467.

Received June 22, 1978; revision accepted November 8, 1978.

Circulation 59, No. 4, 1979.
Exercise Stress Testing

All stress testing was done using a maximal treadmill Bruce protocol\(^7\) with monitoring of leads \(V_4\) and \(aV_e\). The medical regimen for each patient was noted; propranolol was not withheld before stress tests. Before surgery all patients had chest pain during the exercise test, and exercise was stopped when either severe angina occurred, the systolic pressure or heart rate failed to rise with increasing exercise load, or significant ventricular arrhythmias occurred (couplets or bigeminy). When the stress tests were repeated 3–4 months after surgery, exercise was terminated when each individual reached his physiological maximal exercise.

A positive ECG change was defined as greater than 1.5 mm ST depression (flat or downsloping) for 0.08 second. The double product was calculated as the product of systolic pressure and heart rate and is expressed in mm Hg beats/min. The resting 12-lead ECG was used to record the presence of Q waves for electrocardiographic evaluation of infarction.\(^8\) At the time of the stress test a history of previous myocardial infarction was considered to be present if typical electrocardiographic and enzyme changes were documented either by the referring cardiologist or on previous charts from this hospital.

Thallium-201 Scintigraphy

In 80% of the patients, exercise tests had been performed several weeks or months before scintigraphic study. This knowledge guided the timing of the \(201\)TI injection since we could determine the stage at which a positive ECG response occurred. At the exercise end point, as defined above, 1.5–1.8 mCi of thallium chloride (New England Nuclear) was administered as a bolus through a forearm plastic catheter, followed by a 15-ml normal saline flush while the patient continued exercising for another minute.

Imaging was begun within 10 minutes with an Anger gamma camera (Dymax; Elscint, Haifa, Israel) using an all-purpose collimator. We collected 500 thousand counts per scintigram with the peak energy setting at 70 kev and a 30% window. Four views were recorded, beginning with a 45° left anterior oblique, followed by 60° left anterior oblique, anterior and left lateral views. All imaging was done within 45 minutes after the \(201\)TI injection. Reperfusion resting scintigrams were obtained 4 hours after exercise. The trilens Polaroid analog scintigrams of these patients and those of other unselected routine cases were interpreted by four readers without knowledge of the history, ECG stress test or angiography. At least three and usually all four readers agreed on the final interpretation. Among the four readers, interobserver agreement for scintigraphic interpretation of infarction was noted in 93% of patients and for ischemia the agreement was 89%. In all scintigraphic studies perfusion defects were evaluated both during stress and rest in nine areas of the myocardium. These nine regions (fig. 1) represent standard anatomic correlations for the four views and permitted accurate record keeping for longitudinal comparisons. Small defects were confirmed in at least two views before being considered reportable. For example, figure 1 shows that the inferior wall (area 9) can be evaluated in all four views and the septum (area 1) in three views. Ischemia was defined as a defect noted only immediately after stress but not 4 hours later, while infarction was reported if the defect persisted into the reperfusion scan. The combination of infarction and ischemia was a common scintigraphic interpretation and a normal scan demonstrated neither resting nor exercise defects.

Surgical Findings

The surgeons carefully record the presence and location of myocardial scar tissue observable at the time of coronary bypass surgery. The operative reports of each patient who had saphenous vein aorto-coronary bypass surgery were reviewed to assess the presence of large epicardial scars, and the degree of...
Revascularization. A complete revascularization was defined as bypass of all significant obstructions in the major vessels.

Since all patients were asymptomatic when tested 3–4 months after surgery, repeat cardiac catheterization and coronary angiography were not routinely performed.

Statistics

Significant differences between means were calculated using t distribution and, where applicable, the Fisher chi square was used to test the significance of the different rates of occurrence among patient groups.

Results

Thirty patients, mean age 56 years, of whom 26 were males, comprise the study group. All were in functional class II–IV (New York Heart Association), had triple-vessel disease (three had non-dominant right coronary arteries), and all had a positive ECG exercise test except one, who had a left bundle branch block with severe angina and ventricular arrhythmia at stage I of the protocol.

The patients were analyzed as two groups based on the results of their initial stress and reperfusion \(^{201}\)TI scintigraphy. Group 1 included 21 patients who had \(^{201}\)TI scans demonstrating ischemia, while group 2 included nine patients without evidence of ischemia by \(^{201}\)TI. Thus, the sensitivity of the \(^{201}\)TI scan for ischemia in a population with triple-vessel disease and a positive ECG stress test was 70%. Table 1 shows the data for the two patient groups and figures 2–5 are representative scintigrams. The two groups were
similar; there were no statistical differences in mean age, ejection fraction, and double product at the end stage of exercise. Sixty-seven percent of patients were being treated with propranolol, and the comparative doses between the groups were similar. The double products achieved by patients in group 2 tended to be higher during exercise than those in group 1, but the difference between the means was not significant. The chi square test did not reveal any difference between groups in the prevalence of increased end-diastolic pressures, presence of collaterals, or the presence of previous infarction as assessed by history, ECG, ventriculography or $^{201}$TI resting scintigrams. In addition, no significant difference was noted in the average degree of arterial stenosis in group 1 (90%) and group 2 (87%), and all patients had at least two vessels with lesions causing greater than 90% stenosis.

Figure 2. Case 25. Demonstration of a normal post stress (left) and reperfusion scan (right) in the anterior, 45° left anterior oblique (LAO) and left lateral views. In the 60° LAO view there is a small defect in the septal area (area 1) in both post-stress and reperfusion scintigrams. However, since this small defect is not confirmed on any other view, we concluded that the scan is normal.

Figure 3. Case 6. A) Ischemia in the septum and apex (areas 1 and 3) in all three views. The post-stress scan defects (left) are no longer present after 4 hours (right). B) After surgery, the repeat stress and reperfusion scan demonstrates a conversion to a normal study.
Infarction was detected by Thallium-201 in 18 (86%) of the patients in group 1 and six (67%) of the patients in group 2. Therefore, of the 30 patients, 80% had infarction diagnosed by Thallium-201, while only nine (30%) had Q waves on the resting ECG, 14 (47%) showed segmental left ventricular wall akinesis and 16 (53%) had a history of infarction. Eighty-three percent of the infarcts by scintigraphy involved the inferior wall. Table 2 shows the correlation between scintigraphy and surgical findings. The location of epicardial scars in all 13 patients was as predicted by the Thallium-201 scans. In these same 13 cases Q waves were present in five, and six patients had akinetic wall motion on angiography. Of the four patients with infarction diagnosed by Thallium-201 but not corroborated at surgery, one was expected to have scar tissue by all other criteria (history, ECG and ventriculogram) and another had a positive history of infarction.

Fifteen of 20 surgical patients had repeat ECG stress tests and Thallium-201 scans 3-4 months after surgery. All patients reported to be completely revascularized had no ECG or enzymatic evidence of perioperative infarcts and subsequent Thallium-201 scintigrams did not suggest new infarction. Table 3 is a comparison of the results of ECG stress tests and Thallium-201 scintigraphy before and after surgery and also attempts to correlate these results to the degree of revascularization. The end point in all repeat tests was the leveling of heart rate or systolic pressure, and only one patient experienced mild chest pain. Each patient had an improved double product, and there was a mean increase of 9.1 mm Hg beats/min ± 5.2 SD × 10^4 (p < 0.001). There were no observed differences in the double product among postoperative patients who failed to show ECG or Thallium-201 evidence for ischemia compared with those who continued to show ischemic changes. Of the 13 patients who initially had scintigraphic and ECG evidence of ischemia, six no longer demonstrated an ischemic response and had total revascularization. Two other patients with reports of complete revascularization still had ischemic responses by Thallium-201. Five patients with ischemia preoperatively detected by both methods had incomplete

<table>
<thead>
<tr>
<th>Table 2. Diagnosis of Infarction by Thallium-201 Correlated with Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total surgical population</td>
</tr>
<tr>
<td>Thallium-201 evidence of infarction</td>
</tr>
<tr>
<td>Presence of epicardial scars</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Follow-up Noninvasive Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative stress results</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Group 1</td>
</tr>
<tr>
<td>13 pts Ti+, 13ST+</td>
</tr>
<tr>
<td>1 pt Ti-, ST+</td>
</tr>
<tr>
<td>3 pts Ti-, ST+</td>
</tr>
<tr>
<td>3 pts Ti+, ST+</td>
</tr>
<tr>
<td>Group 2</td>
</tr>
<tr>
<td>2 pts Ti-, ST+</td>
</tr>
</tbody>
</table>

Abbreviations: Ti+ = thallium-201 evidence for ischemia; Ti- = no thallium-201 evidence for ischemia; ST+ = ECG evidence for ischemia; ST- = No ECG evidence for ischemia.
but ischemic preoperative scintigraphic was the myocardial region of revascularization, and all had a postoperative ischemic response by ECG and/or $^{201}$TI. In three of the four patients with persistent postoperative ischemia by $^{201}$TI, the ischemic area corresponded to the myocardial region that was not revascularized and was the same area initially interpreted as ischemic on the preoperative scintigraphic evaluation.

Repeat $^{201}$TI scintigraphy was also compared with initial scans for infarct location. The 13 patients with infarcts shown by $^{201}$TI before surgery had no change in this pattern. However, one of two patients who had no infarction detected by $^{201}$TI before surgery and was not completely revascularized showed a persistent defect in the post-surgical scintigraphic evaluation. This defect was associated with enzymatic and ECG evidence suggestive of a perioperative infarct.

**Discussion**

**Ischemia**

Evidence of ischemia by stress $^{201}$TI scanning occurred in only 70% of the patients. This finding does not suggest that the ECG method was more sensitive than $^{201}$TI, since the case selection excluded patients with negative ECG stress responses. It does confirm the fact that $^{201}$TI stress testing cannot always be relied on to exclude significant coronary artery disease. From previous reports we analyzed the data on cases that were similar to this study population. We found that Bailey et al. $^3$ reported 11 cases with triple-vessel disease and a positive ECG response, 10 of whom had new $^{201}$TI defects with stress. Botvinick et al. $^2$ found six or seven out of seven patients who had new defects with $^{201}$TI. Rosenblatt et al. $^{17}$ had only two such cases, and neither displayed ischemia by $^{201}$TI. Our larger experience with this specific patient group suggests a sensitivity for $^{201}$TI ischemia which approximates that noted in an earlier study of 23 patients with triple-vessel disease and $^{201}$TI scintigraphy by Rouleau et al. $^{10}$

In the analysis of group 1 and 2, there appeared to be no specific parameter in the data presented in table 1 to explain why any patient would or would not demonstrate ischemia by $^{201}$TI scanning. The use of a single stress and reperfusion study raises the problem of detecting ischemia by $^{201}$TI in the presence of scar. This problem is probably not present, since group 1 had both ischemia and a high incidence of infarcts detected by $^{201}$TI. Furthermore, there is no a priori reason to suggest that reperfusion should be completed within 4 hours. However, only one patient in group 2 had an infarct by $^{201}$TI scan that was not suggested by other independent methods and, if this single patient were to be classified as having delayed reperfusion, it still would not markedly alter the distribution of the two groups. Another possibility that cannot be excluded is global myocardial underperfusion in triple-vessel disease that may account for nonvisualization of regional perfusion defects. $^{10, 11}$ However, we cannot explain why group 2 rather than group 1 patients had global ischemia when the patient population otherwise appears to be homogenous.

Finally, the intrinsic resolution of the imaging system for $^{201}$TI$^8$ and the subjective nature of the reader’s interpretation of the scan may combine to decrease perception of small defects.

**Infarction**

Several authors $^{11, 19-23}$ have shown excellent correlation with resting or reperfusion $^{201}$TI defects and myocardial infarction as detected by Q waves on the ECG. Using our $^{201}$TI reperfusion imaging technique as evidence for infarction, we detected 80% infarction in our patients, while Bailey et al. $^5$ reported 64% infarction by $^{201}$TI in their 11 patients with triple-vessel disease and a positive ECG stress test. Since all our patients with an epicardial scar at surgery had a persistent defect with $^{201}$TI, the scintigraphic technique may have a sensitivity of 100% for myocardial scars. Specificity cannot be defined, since the use of epicardial scars for the independent corroboration of infarction cannot establish criteria for false positive images. There are two possible explanations for the four cases of $^{201}$TI infarction without surgical confir-
mation. One is that there may be intramural damage or transmural scar tissue that the surgeon does not discern. Another explanation has been recently suggested by Wackers et al., who have reported resting perfusion defects as evidence of ischemia in patients with unstable angina. These four cases may, therefore, represent severe ischemia that has not yet completely reperfused within 3-4 hours. All four defects occurred at the apical-inferior area, which was also noted in 85% of the scintigram infarcts confirmed at surgery. This suggests that this region is particularly vulnerable in triple-vessel disease. The apical-inferior myocardium could be evaluated in all four imaging views, and defects in this area could be confirmed with greater assurance.

Follow-up After Surgery

Since all patients had relief of their anginal syndrome, regardless of the degree of surgical revascularization, the repeat ECG and 201TI stress testing permitted an objective evaluation for ischemia. The significant increase in the postoperative pressure-rate double product is of questionable importance, as it has been reported to occur in spite of total graft occlusions. We observed that complete revascularization is suggested when both techniques no longer demonstrate ischemic responses. However, other symptomless patients with postoperative 201TI or ECG evidence of ischemia usually had un bypassed coronary lesions. Furthermore, the demonstration of persistent ischemia in four patients by either 201TI or ECG, but not with both, suggests that the two methods detect ischemia with a different specificity. The stress results after surgery are similar to those of Ritchie et al., but, in the absence of post-bypass angiograms, the postoperative relationships of these tests to adequacy of bypass are tentative. Our observations emphasize the need to have both pre- and postoperative stress and resting studies of both 201TI and ECG for optimal follow-up.

McLaughlin et al., have demonstrated the ability to reproduce consistent ischemic results with 201TI scintigraphy, but others have reported resting defects disappearing after coronary bypass surgery. Our results on repeat postoperative scans show that all initial infarcts were again demonstrated.

Our study clarifies several points: 1) negative stress 201TI scintigrams can occur with ECG evidence of ischemia in severe three-vessel coronary artery disease; 2) resting 201TI scanning appears to be more sensitive than the ECG or the ventriculogram for detecting myocardial scars in patients with severe triple-vessel disease; 3) the postoperative return to normal of a preoperative ischemic pattern on both 201TI and ECG stress tests is suggestive evidence for adequate revascularization.

Thallium rest and exercise imaging is a useful adjunct in the diagnosis and follow-up of patients with severe three-vessel coronary artery disease, and need not have the same sensitivity nor connotation as the ECG evaluation.

References

Clinical Implications of the Technetium-99m Stannous Pyrophosphate Myocardial Scintigraphic “Doughnut” Pattern in Patients with Acute Myocardial Infarcts

ROBERT E. RUBE, M.D., ROBERT W. PARKEY, M.D., FREDERICK J. BONTE, M.D., SAMUEL E. LEWIS, M.D., DONALD TWIEG, PH.D., L. MAXIMILIAN BUJA, M.D., AND JAMES T. WILLERSON, M.D.

SUMMARY Forty-five patients with acute myocardial infarcts had technetium-99m stannous pyrophosphate (99mTc-PYP) myocardial scintigrams with radionuclide uptake localized to the anterior or lateral wall of the left ventricle in a pattern resembling a doughnut (intense peripheral uptake and relatively less central uptake). Sixty-seven percent of these patients developed left ventricular failure with infarction. Twenty-six patients with acute anterior or lateral myocardial infarcts were selected for comparison because of 99mTc-PYP scintigrams which were more homogeneously positive. There were no significant differences in age, sex or electrocardiographic location of infarction. In-hospital left ventricular failure in Killip classes II, III or IV was more common in the group with doughnut scintigrams. Estimates of infarct size by scintigraphic planimetry and analysis of peak serum creatine kinase levels indicated larger infarcts in the group with doughnut scintigrams.

A doughnut 99mTc-PYP myocardial scintigraphic pattern identifies a relatively large myocardial infarct that is probably associated with developing or worsening left ventricular failure. Further knowledge of the factors determining the development of this, rather than other scintigraphic abnormalities, and of the mechanism of filling in of the central defect of this "doughnut" in some patients, may help us understand certain aspects of the pathophysiology of acute myocardial infarcts.

MYOCARDIAL IMAGING with technetium-99m stannous pyrophosphate (99mTc-PYP) is recognized as a sensitive means of detecting acute myocardial infarction (MI) in both experimental animals and patients. In addition to its use in diagnosing acute MI in the coronary care unit, the technique has also been used to recognize infarction occurring in association with surgical myocardial revascularization procedures. Several groups have attempted to use 99mTc-PYP scintigraphic data to determine the size of infarcts and to predict complications early in the course of infarction.

In dog models of anterior infarction caused by proximal occlusion of the left anterior descending coronary artery, we have noticed a characteristic scintigraphic pattern of radionuclide uptake identified by intense 99mTc-PYP uptake peripherally, and less uptake in the central zone of infarction. We realized, as have others, that this "doughnut" defect is also occasionally seen in patients with acute MI — usually transmural infarcts of the anterior or anterolateral walls. In this study we reviewed clinical and scintigraphic data in patients with acute MI and this doughnut pattern of 99mTc-PYP uptake to determine the clinical, prognostic and anatomic implications of this scintigraphic abnormality.

Materials and Methods

All 99mTc-PYP myocardial scintigrams obtained from January 1, 1976 through May 31, 1977 in the coronary care unit or nuclear medicine suite at Parkland Memorial Hospital, Dallas, Texas, were reviewed. We identified 48 patients who had at least one positive 99mTc-PYP scintigram with a doughnut pattern of uptake (fig. 1). Adequate clinical records were located for 45 of these patients. In a similar...
Thallium-201 myocardial scintigraphy in patients with triple-vessel disease and ischemic exercise stress tests.
J Leppo, T Yipintsoi, R Blankstein, R Bontemps, L M Freeman, L Zohman and J Scheuer

Circulation. 1979;59:714-721
doi: 10.1161/01.CIR.59.4.714

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1979 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/59/4/714