Serial Thallium-201 Myocardial Imaging After Dipyridamole Infusion: Diagnostic Utility in Detecting Coronary Stenoses and Relationship to Regional Wall Motion

JEFFREY LEPOPO, M.D., CHARLES A. BOUCHER, M.D., ROBERT D. OKADA, M.D., JOHN B. NEWELL, B.A., H. WILLIAM STRAUSS, M.D., AND GERALD M. POHOST, M.D.

SUMMARY After a 4-minute i.v. dipyridamole infusion, 0.14 mg/kg/min, serial thallium-201 scans were obtained in 60 patients undergoing cardiac catheterization. Forty patients had significant (≥ 50% stenosis) coronary artery disease (CAD), and 20 patients had normal coronary arteries or trivial lesions. The images were graded qualitatively for thallium activity by three observers. Sensitivity was 93% (37 of 40) and specificity was 80% (16 of 20). The sensitivity and specificity of the thallium-201 study were not affected by the extent of CAD, the presence of Q waves, or propranolol therapy. Twenty-seven of 37 patients who had initial defects (73%) had complete thallium redistribution of one or more defects. Patient-by-patient analysis using a regression model of all patients showed that the fate of a segmental thallium defect predicted abnormal wall motion by angiography better than ECG Q waves. The presence of propranolol therapy or collaterals did not significantly affect the thallium redistribution results.

We conclude that qualitative interpretation by multiple observers of thallium images after dipyridamole infusion is a highly sensitive and specific test for CAD. After dipyridamole, as with exercise stress, the extent of thallium redistribution is related to the degree of myocardial wall motion abnormality.

PREVIOUS STUDIES have shown that exercise thallium-201 myocardial imaging can detect coronary artery disease (CAD).1-6 In addition, thallium-201 redistribution shown by serial imaging can identify ischemic but viable myocardium.7-10 However, a standard maximal exercise stress test is not always possible for various reasons, including therapy with β blockers, unstable anginal symptoms, poor physical condition, and peripheral vascular disease. A method for evaluating myocardial perfusion and viability that does not require exercise would be valuable.

Gould and co-workers11-13 reported that dipyridamole given intravenously could lead to coronary vasodilation in normal vessels, but fixed coronary stenoses prevented or attenuated this response. The coronary flow response to dipyridamole was similar to that during exercise, but without the physiologic increase in myocardial oxygen demand. These and other investigators14-16 have shown that in conjunction with a dipyridamole infusion, thallium-201 scans reliably detect CAD.14-16 However, the significance of changes in thallium-201 distribution over time after dipyridamole infusion has not been investigated, and the impact of propranolol on the dipyridamole thallium-201 study has not been defined.

Therefore, we sought to determine the significance of changes in thallium-201 distribution over time after dipyridamole infusion. We also evaluated the accuracy of serial dipyridamole thallium-201 images in detecting CAD and assessing myocardial viability in terms of regional wall motion. Finally, we investigated the effects of propranolol and collaterals on the scintigraphic observations.

Methods

Patients

Sixty consecutive patients with chest pain syndromes referred for coronary angiography were studied. Each patient gave written, informed consent. No patient had associated heart disease. Coronary angiography and scintigraphy were performed within 48 hours of each other in all but four patients. The longest time between studies was 14 days. The patients were divided into two groups: 20 patients who had trivial or no coronary artery lesions and normal left ventriculograms and 40 patients who had significant CAD.

Dipyridamole Infusion and Thallium-201 Imaging

The imaging protocol (fig. 1) is a modification of the technique described by Albro et al.13 Each patient was placed supine on a tilt table. A 20-gauge plastic cannula was placed in a large antecubital vein, as infusing dipyridamole into a small vein is painful. Twelve-lead ECGs and blood pressure measurements were obtained at baseline and at 1-minute intervals during the first 15 minutes of the study. The ECG was continuously monitored on an oscilloscope. While the patient was supine, i.v. dipyridamole (Boehringer-Ingelheim) was infused at a rate of 0.14 mg/kg/min for 4 minutes. After the infusion, the patient was tilted upright to 70° and 3 minutes later 1.5-2.0 mCi of i.v. thallium-201 (New England Nuclear) were injected. The patient was returned to the supine position 1 min-
ute after the thallium injection, and myocardial images were collected immediately and again 150–180 minutes after the thallium injection. Parenteral aminophylline (250 mg) was available to reverse significant side effects of the dipyridamole infusion.

Myocardial imaging was performed in the anterior, 45° left anterior oblique and 70° left anterior oblique views initially and 2.5–3 hours after thallium-201 administration. The images were recorded for 8 minutes with a standard scintillation camera equipped with a high-resolution, parallel-hole collimator and interfaced with a mobile MDS computer system (MUGA-CART, Medical Data Systems). All images were recorded using 68–80 keV mercury x-ray peak of thallium-201 and collected in a 128 × 128 matrix.

Analysis of Thallium-201 Images

The thallium-201 images were interpreted from a computer display. The initial and delayed, unprocessed images were displayed side by side for comparison. Each image was interpreted by three independent observers without knowledge of the patient’s cardiac catheterization findings or clinical history. The left ventricle in each view was divided into three segments (fig. 2). Tracer activity in each segment was subjectively graded as 0, 0.5, 1.0, 1.5 or 2.0, as previously described.17 (A value of 2.0 represents the most intense thallium-201 activity and zero represents no activity.) The three observers’ scores for each segment were averaged; this procedure maximizes the overall accuracy of interpretation. Segmental defects on thallium-201 myocardial scans were defined as initial mean scores of less than 1.5 in all but the apical regions, as previously reported.17 The criteria for transient defects were modified to permit an intermediate category (partial redistribution) for comparison with segmental wall motion observations. The extent of thallium redistribution in initial defects was defined by the delayed mean segmental score. If the mean segmental grade increased by at least 0.5 and was 1.5 or greater, it was interpreted as a transient defect (complete redistribution); delayed segmental scores of 1.1–1.4 were interpreted as partial redistribution and final segmental grades of 1.0 or less were interpreted as persistent defects (no redistribution).

Catheterization Data

Cardiac catheterization was performed using the Sones or Judkins technique. The coronary angiograms were interpreted independently by two experienced observers without knowledge of the scan findings. Each major coronary artery was examined, and the presence or absence of a lesion was noted. If a stenosis was present, the maximal percent luminal diameter narrowing was recorded. CAD was considered significant if at least 50% narrowing in a major coronary arterial branch was observed in at least two angiographic projections. The presence of collateral vessels was noted on each angiogram.

Left ventriculograms were obtained in all patients in a 30° right anterior oblique projection and in 51 of the 60 patients in a 60° left anterior oblique projection. Regional wall motion was qualitatively graded in three segments matched as closely as possible to the segmental distribution used to grade the thallium-201 images as normal, hypokinetic, akinetic, or dyskinetic.18 Differences of opinion concerning the angiographic results were resolved by consensus.

Statistical Analysis

The sensitivity and specificity of the dipyridamole thallium-201 tests were defined as follows: sensitivity

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Dipyridamole protocol used for patient study. The total dose of dipyridamole was 0.56 mg/kg over 4 minutes. BP = blood pressure.

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Schematic representation of the thallium-201 myocardial scans in three views. The grading scheme for the segments (left) and the delayed mean segmental score (right) used to define complete redistribution (RD), partial redistribution (PRD) and no redistribution (NRD) are shown below.
true-positive tests/(true-positive tests + false-negative tests); specificity = true-negative tests/(true-negative tests + false-positive tests). Thallium redistribution and wall motion findings were compared using two methods. A nonlinear, stepwise logistic regression analysis was used to evaluate the relationship between serial thallium-201 myocardial imaging and left ventricular wall motion in each patient. To help define myocardial viability, left ventriculography was used to classify wall motion in each patient as normal or asynergic. Left ventricular asynery was defined by the presence of segmental akinesis or dyskinesis. The statistical approach required that a positive value be associated with the prediction of asynery, which is the reverse of the tracer uptake grading score outlined above. The segmental thallium-201 scan results in each patient were arbitrarily assigned a value: 0 = normal, 1 = complete redistribution, 2 = partial redistribution, and 3 = no redistribution. Therefore, the sum of these segmental (n = 9) values in each patient represent a total scan score for the prediction of asynery.

The baseline ECGs obtained at the time of imaging were analyzed for evidence of myocardial infarction using the criteria of Lipman et al. The presence of collaterals and propranolol therapy were also included as variables in this analysis. Thus, for each patient, wall motion (asynery or not) could be compared with the overall scintigraphic and electrocardiographic results, and the impact of propranolol and collaterals could be evaluated simultaneously. To evaluate the individual segmental correlation of the thallium-201 and wall motion findings, corresponding scintigrams and angiograms were compared, as previously described. Segmental wall motion and thallium-201 results were evaluated using a two-way frequency table and Pearson chi-square analysis.

Hemodynamic changes were evaluated by analysis of variance and covariance with repeated measures; the Bonferroni correction was used for multiple comparisons. Fisher’s exact test was used to determine the significance of differences in the rates of occurrence such as the distribution of symptoms associated with dipyridamole infusion. All other comparisons between groups of a single numeric variable were performed by an analysis of variance and resultant t statistic. All results are expressed as mean ± SEM.

### Table 1. Characteristics of the Patient Population

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Male/female</th>
<th>Age (years)</th>
<th>No. pts taking propranolol</th>
<th>Propranolol dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>20</td>
<td>4/16 (20%/80%)</td>
<td>43 ± 4</td>
<td>10 (50%)</td>
<td>102 ± 17</td>
</tr>
<tr>
<td>CAD</td>
<td>40</td>
<td>35/5 (88%/12%)</td>
<td>54 ± 1</td>
<td>34 (85%)</td>
<td>162 ± 22</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>39/21 (65%/35%)</td>
<td>50 ± 2</td>
<td>43 (72%)</td>
<td>146 ± 17</td>
</tr>
</tbody>
</table>

Age and propranolol values are mean ± SEM.

*P < 0.05.

**P < 0.01.

Abbreviations: CAD = coronary artery disease.

### Results

**Patient Population**

Table 1 shows propranolol therapy, sex distribution, and mean age in the two groups. The CAD patients were significantly more likely to be male, older, and taking propranolol (although the average dose was similar to that in the normal group). Of the 40 patients with significant CAD, 16 patients had one-vessel disease, 12 patients had two-vessel disease, and 12 had three-vessel disease. None had disease of the left main coronary artery.

**Clinical Response to Dipyridamole**

There were significant changes over time in the heart rate and blood pressure during the dipyridamole protocol (table 2, fig. 3). The heart rate increased significantly in all patients, but the response was more marked in patients not taking propranolol. The increase in heart rate was not related to the presence of CAD. The mean heart rate in patients taking propranolol increased from 62 ± 1 beats/min at control to 71 ± 2 beats/min during the dipyridamole infusion. After the tilt up, heart rate increased to 75 ± 2 beats/min at minute 5 and peaked at 77 ± 2 beats/min at minute 6, before returning toward baseline values. The mean heart rate in patients not taking propranolol increased continuously from 71 ± 2 beats/min at control to 89 ± 3 beats/min during the dipyridamole infusion. Immediately after the tilt up, heart rate increased to 98 ± 4 beats/min at minute 5 and peaked at 102 ± 5 beats/min at minute 6, before returning toward baseline value. In the 44 patients taking propranolol (34 with and 10 without CAD), the mean heart rate increased an average of 32 ± 4%, while in the 16 patients not taking propranolol, the mean increase was 40 ± 7%. In both groups, the individual increases in heart rate varied widely.

During dipyridamole infusion with the patient supine, the mean systolic and diastolic blood pressures decreased from 123 ± 2/81 ± 1 to 120 ± 2/78 ± 1 mm Hg. Immediately after the tilt up, both pressures decreased more dramatically, to 112 ± 3/73 ± 2 mm Hg, before returning to baseline values. The mean percent decrease in blood pressure was 8 ± 2% for systolic and 9 ± 2% for diastolic. The blood pressure changes were not affected by propranolol therapy or...
the presence of CAD. Although systolic blood pressure decreased, the mean double product (heart rate × systolic blood pressure) during this protocol increased by 29 ± 9% in patients taking propranolol and 21 ± 11% in patients not taking propranolol (p < 0.0001). In patients with scintigraphic results that were discordant with coronary angiography (i.e., false-negative or false-positive results), their hemodynamic results were not significantly different from those in patients with concordant results.

### Adverse Effects of Dipyridamole

Table 3 presents the occurrence of adverse effects of dipyridamole among all patients and in the CAD and normal groups. The normal group had a higher incidence of transient headaches (independent of propranolol therapy) than the CAD patients (35% vs 13%), but all other side effects were comparably distributed between the two groups. Symptoms were noted in 43% of the studies, and in five patients (19% of those with symptoms) these were severe enough to prompt i.v. administration of aminophylline to reverse the action of dipyridamole. Aminophylline was given to one normal patient for nausea, to three CAD patients for angina, and to one CAD patient to reverse hypotension (80/60 mm Hg) that persisted after the patient was returned to the supine position. In these five patients, the onset of symptoms was near the end of or after the dipyridamole infusion so that the thallium-201 could be injected and circulate for 1 minute before the dipyridamole effect was reversed.

Eight CAD patients had angina during the protocol; five had three-vessel, two had two-vessel and one had one-vessel CAD. The extent of CAD differed significantly from that in the 32 patients who did not have angina (seven had three-vessel, 10 two-vessel and 15 one-vessel disease; p < 0.01). Five of the eight CAD patients who had angina had ST-segment depression on the ECG. The three CAD patients who were given aminophylline had ST-depression and three-vessel disease; and two of them had angina at rest, which suggests that patients with unstable angina may experience more severe symptoms. The heart rate, blood pressure and double product in patients who had angina were not significantly different from those in patients who did not have angina.
Three normal patients had ECG changes: biphasic T-wave alterations in two and 1 mm of ST-segment depression in another, all without chest pain. No patient had atrial or ventricular arrhythmias.

**Sensitivity and Specificity for Angiographically Significant Coronary Artery Disease**

Qualitative interpretation of thallium-201 images immediately after dipyridamole demonstrated 41 studies with one or more segmental abnormalities: 37 of 40 (93%) in the CAD group and four of 20 (20%) in the normal group (i.e., sensitivity 93% and specificity 80%). Two of the patients with a false-negative result had one-vessel disease and one patient had two-vessel disease. Only the patient with two-vessel disease had coronary collaterals and hypokinetic wall motion; the two other patients had normal wall motion. Three of the four patients with a false-positive scan were female, and breast attenuation may have caused the anteroapical segment abnormality noted in two of these studies. A 20% myocardial bridge of the left anterior descending coronary artery in the male patient with a false-positive result may have contributed to the anterolateral and apical segmental abnormalities. Two of the four patients who had false-positive results were taking propranolol.

The extent of CAD, ECG Q waves, collaterals, and propranolol therapy had no significant effect on sensitivity. All 16 patients (100%) who had Q waves and 21 of 24 patients (88%) without ECG evidence of infarction had abnormal thallium scans (NS).

**Analysis of Delayed Thallium-201 Distribution**

Figure 4 shows serial images from three patients who had thallium-201 redistribution and different wall motion findings. Of the 41 patients with initially abnormal scans, 30 (73%) had complete redistribution in at least one segment, seven (17%) had no redistribution (persistent defects), and four (10%) had partial redistribution. These data were evaluated patient by patient using a segmental approach to assess the overall significance of the thallium-201 redistribution. In each patient, the results of serial thallium-201 imaging as well as the presence or absence of ECG Q waves, collaterals, and propranolol therapy were compared with left ventricular wall motion using a stepwise, nonlinear logistic regression, as described above. The dependent variable was wall motion (asynery), and the initial step in the computer model treats all the predicting variables independently. Although a significant chi-square value was noted for each variable, the delayed thallium-201 imaging score yielded a markedly higher value than any other. The chi-square value for the imaging score was 27.2, compared with 11.7 for collaterals, 7.0 for ECG Q waves and 5.4 for propranolol. The next step in the computer analysis included the thallium-201 imaging score into the model, and none of the other variables significantly improved the prediction of abnormal wall motion. In addition, an analysis for an interaction between propranolol and the thallium-201 score failed to demonstrate any significant effect. Therefore, the regression equation for the prediction (p) of asynery in any patient from the delayed thallium-201 imaging score is as follows: Logit (p (asynergic wall motion)) = −1.9 + 0.36 (delayed thallium-201 score). This model demonstrated a sensitivity of 84% and a specificity of 82% using a cutoff value of 0.32 for asynergic wall motion in the population of 60 patients from which the parameters were estimated. The predicted probability of asynery was 13% for a delayed thallium-201 score of 0 and was 23%, 38%, 56%, 72% and 84% for scores of 2, 4, 6, 8 and 10, respectively. An imaging score greater than 10 had a predicted probability of more than 90%.

No significant distribution of collaterals was noted in CAD patients in regard to the extent of thallium-201 redistribution. Of 37 CAD patients with abnormal segments by thallium-201 scanning, 27 had complete redistribution, of whom 18 (67%) had collaterals. Seven of the remaining 10 patients (70%) who did not have complete thallium-201 redistribution had collateral vessels. Figure 5 shows the relationship between asynergic or normal regional wall motion and the fate of thallium-201 redistribution on serial images for 537 segments in 60 patients. There was a significant (p < 0.0001) Pearson chi-square relationship, and the correlation coefficient (r = 0.54) between the scintigraphic and angiographic observations was also significant (p < 0.01). Eighty-five percent of the normal thallium-201 scan segments had normal wall motion and 5% had akinetic or dyskinetic wall motion. Of 74 segments that demonstrated complete redistribution of an initial defect, 74% had normal wall motion and 14% were asynergic. Of 44 segments exhibiting only partial fill-in of an initial defect, wall motion was normal in 45% and akinetic or dyskinetic in 37%. Finally, of 41 segments with persistent defects, 71% had akinesis or dyskinesis and 15% had normal wall motion. (The percentage of thallium-201 segments associated with hypokinetic wall motion is not shown in figure 5.)

Hypokinesis was present in 10% of normal scan segments, 12% of segments showing complete redistribution, 18% of segments with partial redistribution,
and in 15% of segments with persistent defects. There were 72 asynergic segments (dyskinesis or akinesia), of which 45 (63%) demonstrated either partial redistribution or persistent defects on serial thallium-201 scans, while the remaining 27 segments (37%) demonstrated normal thallium uptake or complete redistribution. Of 465 normal or hypokinetic segments, 425 (91%) showed normal thallium uptake or complete redistribution, and 40 (9%) showed partial or no redistribution.

Discussion

The present study showed that in the presence of an initial defect after dipyridamole infusion, the pattern of thallium-201 redistribution, similar to that after exercise, provides evidence of the status of myocardial viability as indicated by wall motion observations.

Clinical Response to Dipyridamole

In this study, we showed that heart rate and double product increased and blood pressure decreased during the dipyridamole thallium-201 protocol. Other investigators have reported similar findings. We also showed that propranolol significantly affected the heart rate response. Although Osbakken et al. suggested that propranolol might reduce the sensitivity and specificity of exercise thallium-201 scintigraphy, we found no such interaction with dipyridamole thallium-201 imaging. McLaughlin et al. suggested that the heart rate response appears to affect the accuracy of the exercise thallium-201 study, but it appears to have no such impact on the dipyridamole study.

In contrast to exercise studies, which typically show a large increase in calculated double product, dipyridamole placed a much milder stress on the heart, which supports previous clinical observations of dipyridamole administration in catheterization studies. Nevertheless, 20% of the CAD patients had angina. This appeared to be related to the presence of multivessel CAD, as five of the 12 patients (42%) with three-vessel disease had angina, compared with only three of 28 patients (11%) with one- and two-vessel disease (p < 0.01). Three patients with three-vessel disease also
had ST-segment depression and needed aminophylline to reverse their symptoms. Ischemic signs and symptoms were promptly relieved with 100-200 mg of i.v. aminophylline, as reported in clinical studies. Although Francisco et al. suggested that dipyridamole infusion might be safe in patients with unstable angina, our experience indicates that this test should be undertaken with caution in patients suspected of having severe CAD, and especially in patients with angina at rest. A likely mechanism for angina is that maximal coronary vasodilatation associated with a severe coronary stenosis may result in regional myocardial flow redistribution or reduction related to decreased perfusion pressure or to a coronary steal phenomenon.

Other side effects noted during our protocol included headache, dizziness, and nausea. Except for a higher incidence of headaches in the normal patients, all side effects were equally distributed. Twenty-six of 60 patients (43%) had some adverse effect, and only five of these 26 patients (19%) required aminophylline. No patient had arrhythmia. Therefore, the use of dipyridamole infusion at the recommended rate appears safe.

Dipyridamole Thallium-201 Imaging for the Detection of Angiographically Significant Coronary Artery Disease

Previous experimental and clinical studies have suggested the value of thallium-201 imaging for evaluating regional myocardial blood flow during pharmacologic vasodilatation. Sensitivity of 67-91% and specificity of 65-100% have been reported. The present study shows the clinical value of dipyridamole thallium-201 imaging in patients with suspected CAD. The use of qualitative interpretation averaging the results of three observers and previously reported segmental criteria that optimize accuracy may explain why sensitivity was slightly higher in the present study than in previous studies that used qualitative consensus interpretation.

The influence of the severity of CAD on dipyridamole thallium-201 imaging has not been reviewed. Sochor et al. reported preliminary data that showed a sensitivity of 79% for this technique in patients without prior infarction, whereas we found a sensitivity of 88%. The effect of the extent of coronary disease and previous infarction on our imaging results is similar to that reported for exercise thallium-201 scintigraphy.

Alterations in sensitivity and specificity of thallium-201 exercise scans have been attributed to the presence of collateral vessels, propranolol therapy, and the adequacy of exercise. These factors do not affect the dipyridamole thallium-201 data. Although propranolol blunted the heart rate response during the dipyridamole infusion, there was no apparent effect on the induced disparity in regional myocardial blood flow. Therefore, dipyridamole thallium-201 imaging is not affected by β blockade and may provide an alternative to exercise thallium-201 studies in patients receiving propranolol therapy.

Thallium-201 Redistribution After Dipyridamole

Thallium-201 redistribution after a vasodilator infusion has been described in a canine model of coronary stenosis. The results of the present study suggest that the factors affecting whether an initial defect fills in after dipyridamole are similar to those affecting exercise studies. The excellent correlation between regional dipyridamole thallium-201 redistribution results and regional wall motion is consistent with observations in exercise myocardial perfusion studies as is the significant superiority of the scan data to the ECG data in predicting akinesis or dyskinesis.

Our qualitative interpretation of serial thallium-201 images after dipyridamole yielded a sensitivity of 84% and a specificity of 82% for detecting asynergy. Thus, a significant probability of abnormal wall motion can be determined by assessing thallium redistribution in initial defects, and normal tracer uptake probably predicts the absence of asynergy. In addition, the number of patients who had complete thallium-201 redistribution was not affected by the presence of collateral vessels. Neither ECG Q waves nor propranolol therapy made a statistically significant contribution beyond that made by thallium-201 alone in predicting abnormal regional contraction. Therefore, considering only the noninvasive variables used in this study, thallium-201 imaging appears to be the best method for evaluating regional myocardial viability.

Although a segment-by-segment analysis showed that the overall relationship between the scintigraphic and angiographic findings was significant, approximately one-third of the akinetic or dyskinetic segments showed normal thallium-201 uptake or complete redistribution of an initial defect. This discordance between thallium-201 and wall motion results has been observed by others and demonstrates the limita-
tions in comparing segmented thallium-201 distribution with regional motion as an indicator of myocardial viability. Some reservations about the correlation of akinesis with myocardial viability have been presented by other investigators, who compared postmortem results or epicardial scars noted at bypass surgery with angiographic observations. Berger et al. reported that thallium redistribution occurred in akinetic segments that had improved wall motion after coronary artery bypass surgery and that thallium-201 uptake improved postoperatively in segments that had persistent defects initially. Spatial resolution and overlap of normal myocardium also affect the ability of thallium-201 imaging to demonstrate a defect. Although there are inherent problems in determining the presence of viable myocardium in a given segment, dipyridamole thallium-201 imaging can be expected to achieve results similar to those in previous scintigraphic studies.

In conclusion, serial thallium-201 myocardial imaging after dipyridamole is a highly sensitive and specific test for CAD that does not require exercise or patient effort and is independent of the presence of the collaterals or propranolol therapy. However, as with exercise studies, the use of delayed imaging to evaluate thallium-201 redistribution allows prediction of myocardial viability with greater accuracy than ECG Q waves. Serial thallium-201 scans after dipyridamole can be interpreted in a manner similar to maximal exercise scans and may prove to be a useful alternative.

Acknowledgment

We express our gratitude for the expert technical assistance provided by William Shea, Daniell Merrill and Maureen McCarthy, as well as the encouragement and technical help of Dr. Allan Green, New England Nuclear, and Dr. Wolf Michaelis, Boehringer Ingelheim, for supplying the dipyridamole (Persantine).

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Serial thallium-201 myocardial imaging after dipyridamole infusion: diagnostic utility in detecting coronary stenoses and relationship to regional wall motion.
J Leppo, C A Boucher, R D Okada, J B Newell, H W Strauss and G M Pohost

doi: 10.1161/01.CIR.66.3.649

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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