Reproducibility of Thallium-201 Myocardial Imaging

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SUMMARY Seventy-six thallium-201 myocardial perfusion studies were performed on twenty-five patients to assess their reproducibility and the effect of varying the level of exercise on the results of imaging. Each patient had a thallium-201 study at rest. Fourteen patients had studies on two occasions at maximum exercise, and twelve patients had studies both at light and at maximum exercise. Of 70 segments in the 14 patients assessed on each of two maximum exercise tests, 64 (91%) were reproducible. Only 53% (16/30) of the ischemic defects present at maximum exercise were seen in the light exercise study in the 12 patients assessed at two levels of exercise. Correlation of perfusion defects with arteriographically proven significant coronary stenosis was good for the left anterior descending and right coronary arteries, but not as good for circumflex artery disease. Thallium-201 myocardial imaging at maximum exercise is reproducible within acceptable limits, but careful attention to exercise technique is essential for valid comparative studies.

RECENT STUDIES have shown thallium-201 to be a promising agent for noninvasive myocardial imaging, and more widespread application is anticipated.1-7 The reproducibility of the technique must be determined, however, before it can be used to assess longitudinal changes in myocardial perfusion, such as those that occur after revascularization surgery. A number of variables can affect the reproducibility of exercise thallium-201 imaging. These include the myocardial uptake of thallium-201, the exercise technique, the methodology of data collection, processing and display, and observer variability in the interpretation of the studies. In this study we assessed the reproducibility of thallium-201 myocardial imaging at maximum exercise. We also assessed the effect of varying the level of exercise on the results of imaging. A consistent and objective method of data collection, processing and display was used along with a method of interpretation designed to minimize the effect of observer variability. In order to establish the significance of perfusion defects noted in the thallium-201 studies, these defects were correlated with the presence and location of coronary artery stenosis — as determined by arteriography — and with electrocardiographic evidence of ischemia.

Methods

Patients

Twenty-five patients with known or suspected coronary artery diseases were referred for study. There were 22 males and three females whose ages ranged from 33 to 71 years, with a mean of 54 years. A medical history, physical examination and standard 12-lead resting electrocardiogram were obtained in all subjects. Eighteen patients had a history of angina pectoris and twelve had a history of myocardial infarction. Twenty-one patients had coronary arteriography and left ventricular cineangiography. The interval from thallium-201 study to coronary arteriography ranged from 0 to 4 weeks in 17 patients, and 6 weeks to 5 months in four patients (mean 1.06 ± 0.31 months). Cardiac catheterization was carried out by standard techniques. Left ventricular cineangiography was performed in the 30° right anterior oblique view. Coronary arteriography was performed by the Judkins technique in at least two views. Left ventricular angiograms and coronary arteriograms were interpreted independently by a cardiovascular radiologist. Coronary artery narrowings 50% or greater of the lumenal diameter were considered significant. In the presence of multiple narrowings in one vessel, the vessel was considered to have significant disease if at least one narrowing was 50% or greater. Ten of the 14 patients with two maximum exercise thallium-201 studies, and eight of the 12 patients with both light and maximum exercise studies had coronary angiography.

Rest and Exercise Radionuclide Studies

All patients had thallium-201 studies in the resting state and after maximum exercise. Fourteen patients had repeat maximum exercise studies one week later. Twelve patients had thallium-201 studies after light exercise one week after their maximum exercise study.

Exercise Techniques

All patients were exercised using a Godart electrical graded cycle ergometer (Model #8652). A symptom-limited test was performed using a multistage intermittent protocol with three minutes of exercise at each workload, followed by one minute of rest. The initial work intensity and increments for succeeding workloads were determined individually for each patient. An attempt was made to select an exercise protocol that would permit each patient to exercise for six to 12 minutes. A 12-lead electrocardiogram was recorded at rest, at each minute of exercise and immediately following exercise on a Hewlett-Packard 3-channel recorder. Indirect brachial arterial blood pressure was measured at rest and at the end of the second and third minutes of each workload, using a mercury sphygmomanometer. During the exercise test, patients were continuously monitored by a cardiologist who recorded signs and symptoms, including the onset and magnitude of angina pectoris. All maximum exercise tests were terminated because of either fatigue or angina pectoris.

Light exercise tests were performed using the same test protocol, except that the highest workload performed by each patient was between 33% and 50% of the highest workload achieved on the maximum test. The resting and exercise electrocardiograms were inter-
Imaging Techniques

All patients fasted for at least four hours prior to the study. A dose of 2 mCi of thallium-201, administered intravenously, was used in all studies. During exercise the thallium was given when the exercise limiting symptom of angina or fatigue was of moderate severity and allowed the patient to continue for two further minutes at the maximum workload. In those patients having two exercise studies, the thallium was given at the same workloads on each occasion.

Data were collected with a scintillation camera (Picker Dyna or Ohio Nuclear camera) set for 80 KeV with a low energy, medium resolution parallel hole collimator. Each patient's studies were performed with the same camera. Data collection was started ten minutes after injection and was continued for five minutes in three subsequent views (anterior, 45° left anterior oblique and left lateral). The minimum number of events collected in each view was 150,000. The data were recorded on Polaroid film directly from the cathode ray display, and were also stored in histogram mode as 64 x 64 digitized images. The digitized images were processed further on a Hewlett-Packard 5407 Scintigraphic Data Analyzer as previously described.6

Processing was designed to minimize the influence of variable background on the interpretation in the following manner. A rectangular area which included the heart was defined on the digitized image. The background was then computed by linear interpolation from the count rates found at the edges of this rectangular area, and the interpolated count rates were subtracted from the image.6 Processed images were then displayed with count density distributed over a fourteen level gray scale.6 Both the Polaroid data and computer processed data were used in the interpretation. Five segments of the left ventricle (anterior, septal, apical, inferior and posterolateral) were analyzed in the three views, as illustrated in figure 1. Each of the five segments in all studies was evaluated for the presence of a defect. All of the exercise studies were compared with the rest studies, and segments were analyzed for the appearance of new defects with exercise. Segments with no defects at rest and exercise were called normal. Segments with defects seen at rest which were unchanged with exercise were interpreted as having fixed defects. Segments which were normal or had defects at rest and developed new or additional defects with exercise were interpreted as having ischemic defects. Fixed or ischemic defects in the anterior or septal segments were interpreted as indicative of left anterior descending disease; in the inferior segment, right coronary disease; and in the posterolateral segment, circumflex disease. Defects in the apical segment were interpreted as compatible with disease in either the left anterior descending or the right coronary arteries depending on the associated defects in contiguous segments.

When all studies for a patient were completed, the images were interpreted by three experienced observers who had no additional clinical information about the patient. Interpretation of all studies in one patient was completed at the same session by the three observers. After the observers had assessed each study, their interpretations were compared. In 60 of the 76 studies there was total agreement using the unprocessed data. In the remaining 16 where some disagreement occurred, reference to the processed data resolved the disagreement and consensus was achieved. Results of thallium-201 studies were then analyzed for reproducibility and correlated independently with the results of coronary arteriography and the exercise electrocardiogram.

Results

In the assessment of reproducibility based on the data obtained during the two maximum exercise tests performed on each of 14 patients, 64 of the 70 segments were identical. In nine patients (45 segments) the two studies were completely reproducible. An example of a case with reproducible defects is shown in figure 2. Twenty-six of the reproducible segments were normal in both tests, 29 demonstrated ischemic defects and nine had fixed defects. Five patients had six nonreproducible segments. In one patient, two segments, septal and apical, were interpreted as ischemic on the first exercise study, and as normal and having a fixed defect, respectively, on the second. Of the remaining four nonreproducible segments in four patients, anterior and apical segments were interpreted as ischemic on the first exercise study but as having fixed defects on the second; and posterolateral and septal segments were interpreted as ischemic on the first study but normal on the second study. Table 1 summarizes the heart rate and rate-pressure product.

![Schematic illustration of the myocardial segments with the corresponding right dominant arterial supply visualized in a thallium-201 study in left (a) the anterior view, (b) the left anterior oblique view (LAO) and, (c) the left lateral view.](attachment://figure1.png)
changes in the 14 patients who had resting and two maximum exercise thallium-201 studies. There were no significant differences in heart rates or rate-pressure products between the group of nine patients with completely reproducible studies and the five patients with one or two nonreproducible segments. Although three of the five patients who developed nonreproducible ischemic segments on the second exercise study had an associated increase in rate-pressure product as a possible cause, this rate-pressure product change did not reach statistical significance. Of the 14 patients undergoing two maximum exercise tests, five had angina and six fatigue as the limiting symptom on both tests; the other three had angina on one occasion and fatigue on the second. This difference in end point does not explain the occurrence of nonreproducible segments since there were none in these three patients.

Table 2 summarizes the heart rate and rate-pressure product changes in the 12 patients who had rest, light exercise and maximum exercise thallium studies. Sixteen perfusion defects developed in nine of these patients on light exercise, seven occurring in segments that were normal at rest. On maximal exercise an additional 14 ischemic defects developed in eight of the patients. Nine of these defects were in segments that were normal both at rest and on light exercise. Eight patients had angina as the limiting symptom on the maximum exercise study.

In table 3 the correlation of perfusion defects on the thallium-201 study with the location of coronary artery

<table>
<thead>
<tr>
<th>TABLE 1. Heart Rate and Rate-Pressure Products in Patients Who Had Two Maximum Exercise Studies</th>
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<tr>
<td>Patients with reproducible Tl-201 studies (9 pts)</td>
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<td>Patients with nonreproducible Tl-201 studies (5 pts)</td>
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*Rate-pressure product = heart rate × systolic blood pressure.
stenosis is outlined for the 31 maximum exercise studies in the 21 patients who had coronary arteriography. Anterior or septal perfusion defects were noted in 93% (25/27) of studies with left anterior descending disease, inferior defects in 100% (24/24) of studies with right coronary or posterior descending disease and posterolateral defects in 48% (12/25) of studies with circumflex disease. In one study a defect was seen in the inferior segment of a patient with a normal right coronary artery but with stenosis in the circumflex artery. In no other studies were defects seen in the absence of significant arteriographic disease.

The resting electrocardiograms were abnormal in eight patients: six had pathological Q waves consistent with previous myocardial infarction, two had abnormal ST changes alone (one of these, however, was taking digitalis) (fig. 3d). In all the patients with pathological Q waves there was a corresponding resting thallium defect. Noeants with normal resting thallium scans had abnormal Q waves.

In table 4 the results of the exercise electrocardiograms recorded during the thallium-201 studies are correlated with the location of coronary artery stenosis. ST-segment changes in leads V_{1} to V_{6} are correlated with disease in the left anterior descending artery, and in leads II, III, and aV_{6} with disease in the right coronary and circumflex arteries. Including the data from the resting electrocardiograms improves the ability to detect disease in the left anterior descending coronary artery from 23 to 24, and in the right and circumflex arteries from 17 to 18. An example of a normal

**FIGURE 3.** Rest and maximum exercise thallium-201 studies in a 59-year-old man with single-vessel disease of the left anterior descending artery. Opposite page) Ischemic defects in the septal and apical segments are indicated by arrows in: top left) the unprocessed data and bottom left) the processed data. The defects are more readily appreciated in the processed data. In the corresponding rest (opposite page, right column) and the exercise (this page, top) electrocardiograms there is significant exercise ST depression in leads II, aV_{6}, V_{4}, V_{6}. Bottom) The coronary arteriograms show the normal right coronary (RCA) and left coronary (LCA) arteries with a 95% stenosis (arrows) of the left anterior descending coronary artery visualized in the right anterior oblique view (above) and left anterior oblique half-axial view (below).
rest and abnormal exercise thallium-201 study is shown in figure 3 with the corresponding coronary arteriograms and exercise electrocardiogram.

**Discussion**

This study indicates that myocardial imaging of patients at maximum exercise with thallium-201 may be expected to yield reproducible results in 90% of segments studied. Completely reproducible studies in any one patient were found in 9 of 14, or 64% of patients. Nonreproducibility is clinically important in two regards. First, it could affect the accuracy of detection of significant coronary disease by thallium-201 imaging. In this study, however, the nonreproducibility of the nine segments in five patients resulted in failure to detect and accurately localize significant disease in only one artery (circumflex) on the less sensitive of the two maximum exercise studies. The remaining nonreproducible segments were all in the territory of the left anterior descending artery in which disease was accurately localized by defects in one of the other segments perfused by this artery. The second clinically important implication is in the application of thallium-201 imaging to the longitudinal follow-up of patients, particularly after interventions such as revascularization surgery. Allowance will have to be made for this 10% nonreproducibility of segments.

The possible reasons for nonreproducibility of thallium-201 imaging are several. Differences in myocardial uptake of thallium-201 on separate occasions could occur even with the same study technique. The importance of this factor will be difficult to assess until an accurate means of quantitation of thallium-201 myocardial uptake is described. The exercise technique utilized in the exercise thallium-201 study is a second factor. In this study a rigorous attempt was made to achieve the same exercise conditions in the two maximum exercise studies. Despite this, there was a 5% mean difference between maximum heart rates and a 12% mean difference between rate-pressure products (table 1). Furthermore, three of the five patients who developed ischemic, but nonreproducible, segments on the second maximum exercise test had an associated increase of rate-pressure product. However, neither the mean differences between the reproducible and nonreproducible groups nor the individual changes in the nonreproducible group were significant. Therefore the nonreproducibility in the maximum exercise studies cannot be readily explained by variability in the exercise technique alone.

To assess the effect of varying the level of exercise, twelve patients had light exercise tests in addition to rest and maximum exercise studies. At light exercise the mean increase in heart rate was 44% of the maximum increase, and the mean increase in rate-pressure product was 42% of the maximum increase (table 2). Only 53% (16/30) of ischemic defects present at maximum exercise in these 12 patients were seen in the light exercise study. Two implications are apparent. Reproducibility of the studies would have been markedly reduced if two studies of differing exercise loads were compared. Secondly, since ischemic defects developed in maximum exercise studies in segments that were normal with light exercise, significant coronary disease could be missed with less than maximum exercise. Defects in both light and maximum studies were correlated with presence of disease in the eight of twelve patients who had the two levels of exercise studies and coronary arteriograms. Nineteen of the 24 major vessels in these eight patients had significant stenosis. Although defects with light exercise always occurred in the territory of diseased arteries, the correlation of perfusion defects with diseased arteries increased from 13 of 19 for light exercise to 17 of 19 for maximum exercise in these patients. Therefore, careful attention to exercise technique is necessary in thallium-201 imaging.

Another source of error in the reproducibility of imaging is the method of data collection. All studies in one patient were performed on the same scintillation camera to minimize unavoidable variability intrinsic in the crystal, photomultiplication system and other electronic components of the scintillation camera. The dose of thallium-201, initiation and duration of data collection after injection were the same in all patients. The count rates achieved in this study, a minimum of 150,000 per view, would be comparable to studies in other institutions that utilize the same 2 mCi dose of thallium-201 and recommended imaging times.

Considerable variation can also exist in the processing and display of data. The unprocessed data recorded on Polaroid film from the cathode ray tube are themselves influenced by several variables, including intensity of the persistence oscilloscope, aperture setting of the Polaroid camera and the film. A new objective method using an interpolative background subtraction technique was uniformly applied to all studies to minimize the influence of variable background.

**Table 3. Correlation of Thallium-201 and Arteriography**

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<thead>
<tr>
<th>LAD</th>
<th>RCA/PDA</th>
<th>CIRC.</th>
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<td>True positive:</td>
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<td></td>
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<tr>
<td>segs.</td>
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<td>25</td>
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<tr>
<td>True negative:</td>
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<td>segs.</td>
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<tr>
<td>4</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
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Abbreviations: LAD = left anterior descending artery; RCA = right coronary artery; CIRC. = circumflex coronary artery; Ant. = anterior; Inf. = inferior; PDA = posterior descending artery; Post. = posterior; Seg. = segments; Nl. = normal; Abn. = abnormal.
counts on interpretation of images. This method allows for nonuniformity of the background contribution assuming monotonic changes in background. Furthermore, a uniform method of displaying the background subtracted count rates on a 14-level gray scale minimizes the variation that can be introduced by change of intensity and aperture settings on Polaroid cameras. The observers found the gray scale presentation a valuable adjunct to the nonbackground subtracted Polaroid images in improving their ability to determine borders and areas of abnormality.

Finally, observer variability is a major factor in the assessment of reproducibility. In this study an attempt was made to minimize this factor by the observers' comparative interpretation of both maximum exercise studies on one patient during the same session. The value of the data processing was apparent in achieving unanimity of interpretation in those cases where some disagreement existed in the assessment of the unprocessed data.

The significance of perfusion defects interpreted by the observers is substantiated by data presented in table 3. In only one instance was a defect noted in a segment which was supplied by a normal artery (table 3). In this patient with an abnormal inferior segment and a normal right coronary artery, the circumflex artery was significantly diseased. This may indicate an overlap of perfusion territory of the circumflex artery into the inferior segment in this patient. All remaining defects occurred in perfusion territories of significantly diseased arteries. The truly positive correlation of defects with arteriographic disease was highest for left anterior descending (93%) and right coronary artery disease (100%), but was lower for circumflex artery disease (48%). The lower correlation for circumflex disease may reflect the fact that territory perfused by the circumflex artery is well seen without superimposition of territories perfused by the other arteries in only one segment (posterolateral) in one view (left anterior oblique).

Table 4. Correlation of Exercise ECG Tests and Coronary Arteriography

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<th>LAD</th>
<th>RCA</th>
<th>CIRC.</th>
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<tbody>
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<td>True positive:</td>
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<tr>
<td>V&lt;sub&gt;1&lt;/sub&gt;-V&lt;sub&gt;4&lt;/sub&gt;</td>
<td>disease</td>
<td>II, III, aVF</td>
<td>disease</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>ST&lt;++&lt;---</td>
<td>Arteriograms</td>
<td>ST&lt;+&lt;---</td>
<td>Arteriograms</td>
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<tr>
<td>V&lt;sub&gt;1&lt;/sub&gt;-V&lt;sub&gt;4&lt;/sub&gt;</td>
<td>normal</td>
<td>II, III, aVF</td>
<td>normal</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>6</td>
<td></td>
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</tbody>
</table>

* [ST] indicates ST-segment depression ≥0.1 mV below the baseline.
† [ST] indicates no significant ST-segment depression.

Significance for the perfusion defects was also suggested by the presence of concomitant ischemic changes on the exercise ECG, although several false positives were noted for the exercise ECG (table 4). Ischemic ECG changes were seen in only three of the nine patients with ischemic defects during light exercise, suggesting that thallium-201 imaging may be more sensitive in detection of ischemia at less than maximal exercise than is the ECG.

In summary, the reproducibility of thallium-201 myocardial imaging at maximum exercise is within acceptable limits for clinical use. The level of exercise achieved can affect the results of the study. Therefore, careful attention to exercise technique is necessary for valid comparative studies.

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Reproducibility of thallium-201 myocardial imaging.
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