Thallium-201 scintigraphy in diagnosis of coronary stenosis

Comparison with electrocardiography and coronary arteriography

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SUMMARY The sensitivity of rest and exercise thallium-201 scintigraphy for the detection of significant coronary artery disease and myocardial ischaemia was compared with rest and exercise electrocardiography in 46 patients with chest pain. Of 26 patients with greater than 70 per cent coronary stenosis, 16 had abnormal rest thallium-201 scintigrams and 13 had Q waves. Myocardial perfusion defects in the resting scintigram correlated very well with evidence of previous myocardial infarction (16 of 17 patients, 94%); significant Q waves were present in 13 of these 17 patients (76%).

After exercise, abnormal thallium-201 scintigrams consistent with ischaemia were found in 21 patients (81%). Abnormal exercise electrocardiograms were present in 15 patients (58%). The combination of abnormal exercise thallium-201 scintigrams or exercise electrocardiograms (23/26, 88%) exceeded abnormal exercise electrocardiograms alone (15/26, 58%). The two procedures were thus complementary. Abnormal rest or exercise thallium-201 scintigrams were obtained in 25/26 patients (96%) compared with abnormal rest or exercise electrocardiograms in 21/26 patients (84%). Twenty patients with less than 50 per cent coronary stenosis had normal rest thallium-201 scintigrams and no Q waves. Two had abnormal exercise thallium-201 scintigrams and 7 had abnormal exercise electrocardiograms. Thus, exercise thallium scintigraphy has higher sensitivity than exercise electrocardiography in detecting exercise induced ischaemia and is more specific. Scintigraphy appears to have a higher sensitivity than electrocardiography in detecting coronary artery disease.

While each of the patients with triple vessel coronary disease had positive exercise perfusion scintigrams and positive exercise electrocardiograms, the thallium-201 scintigram was more sensitive than the rest or exercise electrocardiogram in patients with single vessel disease.

The correlation of thallium perfusion defects at rest and/or exercise with angiographically significant coronary stenosis was higher for the left anterior descending and right coronary arteries than for the circumflex coronary artery.

Myocardial perfusion scintigraphy following the intravenous injection of radionuclides at rest and during peak exercise represents a non-invasive method for the diagnosis of haemodynamically significant coronary artery disease (Zaret et al., 1973b).

1This work was performed while Dr Corne was a Lady Davis Visiting Professor in Medicine at the Hebrew University of Jerusalem.

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The major determinant of the myocardial distribution of cationic tracers such as potassium-43 and thallium-201 is blood flow (Prokop et al., 1974; Strauss et al., 1975). Reduced tracer uptake at peak exercise but not at rest indicates transient myocardial ischaemia. Perfusion defects at rest which do not change with exercise are consistent with myocardial infarction, while rest defects associated with an increased perfusion defect with exercise are consistent with both previous infarction and myocardial ischaemia.
Thallium-201 has generally replaced potassium-43 and rubidium-81 because it has an energy spectrum more favourable for imaging with currently available scintillation cameras, and a longer physical half-life (Bradley-Moore et al., 1975). The thallium-201 scan has been reported to be more sensitive than the exercise electrocardiogram in patients with significant coronary artery disease (Bailey et al., 1977; Ritchie et al., 1977a, b; Botvinick et al., 1978). The present study was undertaken (1) to evaluate rest and exercise thallium-201 myocardial perfusion imaging in the detection of significant coronary stenosis determined by coronary arteriography; (2) to compare the sensitivity of thallium-201 myocardial imaging with rest and exercise electrocardiography; and (3) to correlate the thallium-201 scintigram with the number of coronary arteries involved and with the location of significant coronary stenosis.

**Subjects and methods**

Forty-six patients with known or suspected coronary artery disease were studied. There were 39 men and 7 women, with a mean age of 56 years (range 35 to 74 years). Of the 46 patients, 17 had prior myocardial infarction documented by two or more of the following criteria: (a) typical history; (b) pathological Q waves (duration 0.04 s or greater); (c) characteristic serial enzyme changes (serum creatine kinase and/or aspartate transaminase (SGOT); (d) asynergy on left ventriculography. All patients had a history of chest pain suggestive of angina pectoris at the time of the study.

**Myocardial perfusion imaging**

Myocardial imaging was performed after exercise and at rest. Before starting the exercise study an indwelling catheter was inserted percutaneously into an antecubital vein. The patient exercised on a treadmill according to the Bruce procedure (Bruce, 1971) until he reached his maximal heart rate or developed chest pain or fatigue. Thallium, 2 mCi, was then injected, and the exercise was continued for an additional 60 seconds. The electrocardiogram was continuously monitored throughout the exercise study and during the imaging procedure which was performed in an adjacent room. Imaging began 10 minutes after injection. Rest myocardial images were obtained in two ways: (1) 29 patients were imaged one week before the exercise imaging procedure. Thallium, 2 mCi, was injected intravenously with the patient erect after fasting for 12 hours in order to minimise gastric and hepatic activity. Imaging began 10 minutes after injection; (2) 17 patients were re-imaged 4 hours after the exercise study according to the method of Pohost et al. (1977). Images were recorded in the anterior and 45 degree left anterior oblique position by rotating the detector with the patient supine, and in the left lateral position with the patient on his left side over the detector. Five hundred thousand counts were recorded in each position. An Elscint Model CE-1 scintillation camera (37 photomultiplier tube, 30 cm crystal diameter) equipped with a high resolution parallel hole collimator was used for all studies. Images were recorded with a 20 per cent window centred on 75 keV. Images were recorded on Polaroid film from the camera console and also digitised on line on magnetic disc as 128 x 128 static byte matrix pictures on a PDP1 11/45 computer running the GAMMA 111 nuclear medicine software. Polaroid pictures from the analogue data were flood corrected at the camera console during data collection using a built-in camera feature. Flood correction was performed by software on all computer images after data collection.

All studies were interpreted by two observers who had no knowledge of the angiographic or electrocardiographic findings. Five segments of the left ventricle (septal, anterolateral, posterolateral, inferior, and apical) were analysed using both the Polaroid (unprocessed) data and the computer processed data. Polaroid data were interpreted qualitatively according to the following criteria. Resting images were categorised as (a) normal if there was homogeneous tracer distribution of tracer uptake; or (b) abnormal if there was a focal reduction in tracer uptake in regions which normally have homogeneous distribution of radioactivity. The exercise study was considered positive if a new perfusion defect developed or if there was an increase in the rest defect.

The computer-processed images were displayed in 128 x 128 matrix and activity from equal regions of interest determined from the 5 segments of the left ventricle defined above. A significant perfusion defect was considered present at rest when there was a reduction of 20 per cent or greater in counts between one or more of the anatomical segments of the left ventricle (Strauss and Pitt, 1977). The exercise image was considered positive for ischaemia if a new perfusion defect as defined above appeared after exercise or if there was an increase in a defect also observed in the scintigrams obtained at rest.

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Digital Equipment Corporation.
Thallium scintigraphy

EXERCISE ELECTROCARDIOGRAPHY
Exercise electrocardiography was performed twice in each patient, initially during the clinical evaluation and again for exercise imaging. Standard graded treadmill exercise using the Bruce procedure (Bruce, 1971) was performed until the patient attained his maximal heart rate or developed angina pectoris or severe fatigue. The Frank lead system (Frank, 1956) and praecordial leads V4-6 were employed for monitoring before, during, and for 10 minutes after exercise. The treadmill exercise electrocardiogram was interpreted as positive if 1 mm or greater horizontal or downsloping ST segment depression of duration 0.08 s or more appeared during or immediately after exercise.

CORONARY ARTERIOGRAPHY
Coronary arteriography was performed using the Judkins technique in multiple projections on 35 mm film with a 4j inch mode General Electric image intensifier. Coronary arteriograms were evaluated by an independent observer unaware of the myocardial perfusion image results. The percentage luminal narrowing of each angiographic lesion was measured and the location noted. Stenosis of greater than 70 per cent of one or more of three major coronary arteries was considered haemodynamically significant. Left ventriculography was performed in the right anterior oblique projection in all patients. Results were analysed statistically using the binomial test (Siegel, 1956).

Results
The results of the clinical data, resting and exercise electrocardiograms, thallium-201 myocardial perfusion scintigrams at rest and exercise, coronary arteriography, and left ventriculography are summarised in Table 1 for the patients with 70 per cent or greater coronary stenosis.

MYOCARDIAL PERFUSION SCAN INTERPRETATION
There was complete interobserver agreement in 38 of the 46 cases (84%) using the Polaroid images. Consensus was achieved in the remaining 8 cases using the computer processed data. In 3 of the 38 cases the Polaroid data were considered normal at rest by both observers, while a clinically confirmed defect was shown using the computer processed data.

ANGIOGRAPHY
Twenty-six of the patients had greater than 70 per cent stenosis of at least 1 of the 3 major coronary arteries. Six had single vessel disease, 11 had two vessel disease, and 9 patients had triple vessel disease. The remaining 20 patients had either normal coronary arteriograms or less than 50 per cent stenosis of a major coronary artery. No patient had lesions between 50 and 70 per cent stenosis.

Fig. 1 Normal thallium-201 myocardial perfusion scintigram at rest (upper panels) and exercise (lower panels) in a patient with normal coronary arteries on selective coronary arteriography. ANT, anterior view; LAO, left anterior oblique view; LL, left lateral view.

Fig. 2 A patient with myocardial ischaemia and 95 per cent stenosis of the left anterior descending coronary artery. The thallium-201 scintigram is normal at rest (upper panels). After exercise there is a perfusion defect involving the apex and lower portion of the septum (lower panels).
ANT LAO

Fig. 3. Thallium-201 myocardial perfusion scintigram in a patient with 100% obstruction of the left anterior descending and right coronary arteries. There are focal defects involving the septum, apex, and inferior walls of the left ventricle at rest (upper panels) which are unchanged after exercise (lower panels), consistent with myocardial infarction without ischaemia.

ANT LAO

Fig. 4. A patient with triple vessel coronary disease and a previous myocardial infarction. On the rest injected thallium scintigram (upper panel), there is decreased tracer concentration in the interior wall seen best in the LAO view. With injection at peak exercise (lower panel) the inferior defect becomes more obvious and there is decreased perfusion of the apex (ANT view), septum, and posterolateral walls (LAO view), consistent with myocardial infarction and ischaemia.

ANT LAO

Fig. 5. Thallium-201 myocardial perfusion scintigram 10 minutes after exercise (upper panel) and 4 hours later (lower panel). The decreased tracer concentration 10 minutes after exercise is not present 4 hours later, indicative of myocardial ischaemia. Coronary arteriography revealed 90% per cent obstruction of the left anterior descending coronary artery.

without at least 1 major coronary artery narrowed more than 70 per cent.

Patterns of Thallium-201 Scintigrams
Rest and exercise thallium-201 scintigrams in each patient were compared and classified as follows:
(1) normal rest and normal exercise (Fig. 1);
(2) normal rest and abnormal exercise, indicative of myocardial ischaemia (Fig. 2);
(3) abnormal rest with no change on exercise, consistent with myocardial infarction without ischaemia (Fig. 3);
(4) abnormal rest and abnormal exercise, consistent with myocardial infarction and ischaemia (Fig. 4).
Scintigrams obtained 4 hours after exercise were similar to those obtained at a separate rest study 1 week before exercise. Exercise induced perfusion defects were not present in the scintigram 4 hours later in patients with myocardial ischaemia without infarction (Fig. 5).

Electrocardiography and Perfusion Scintigraphy
The results of the rest and exercise electrocardiograms and the rest and exercise thallium-201 scintigrams are shown in Tables 1 and 2.
Resting thallium defects were present in 16 patients (62%) with significant coronary artery stenosis, while pathological Q waves were recorded
Thallium scintigraphy

Table 1  Data in patients with coronary stenosis

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Abbreviations: MI = myocardial infarction; NYHA = New York Heart Association Functional classification; ECG = electrocardiogram; Q = Q wave > 0.04 s; ETT = exercise tolerance test; **TI, thallium myocardial perfusion scintigram; R, rest; S, exercise; LAD, left anterior descending coronary artery; Cx, circumflex coronary artery; RCA, right coronary artery; wall motion: 0, normal; + 1, hypokinesis; +2, akinesia; +3, dyskinesis; A, anterior; AS, anteroseptal; I, inferior; S, septum; L, lateral; PL, posterolateral; Ap, apex; +, present or abnormal, -, absent or negative.

in 13 patients (50%). Myocardial perfusion defects in the resting scintigram correlated very well with evidence of previous myocardial infarction (16 of 17 patients, 94%); significant Q waves were present in 13 of these 17 patients (76%). Of the 17 patients with documented past evidence of infarction but without significant Q waves in current electrocardiograms, 3 had localised perfusion defects at rest. Of the 16 patients with rest thallium-201 defects, 11 had asynergy whereas of the 13 patients with Q waves, 10 had asynergy.

The proportion of patients with a positive exercise thallium-201 scintigram (21 of 26 patients, 81%) was greater than the proportion with a positive

Table 2  Results of electrocardiogram and thallium-201 myocardial imaging interpretation in 26 patients with > 70 per cent coronary stenosis

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<tr>
<th>Exercise scintigram</th>
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Exercise scintigram

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<td>Sensitivity</td>
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<td>90%†</td>
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* P < 0.05-sensitive exercise scintigram compared with exercise electrocardiography.
† P < 0.05—specificity exercise scintigram compared with exercise electrocardiography.
exercise electrocardiogram (15 of 26 patients, 58%, \( P < 0.05 \)). The sensitivity for the detection of ischaemia was increased when the results of the two procedures at exercise were combined (23 of 26 patients, 88%), being significantly greater than with the exercise electrocardiogram alone (\( P < 0.01 \)).

Of the 26 patients with coronary stenosis greater than 70 per cent, significant Q waves at rest and/or a positive exercise electrocardiogram were present in 21 (81%). Abnormal rest and/or exercise thallium-201 perfusion defects were present in 25 of the 26 patients (96%). The results were unchanged when coronary stenosis greater than 50 per cent was classed as significant.

Each of the 20 patients with normal coronary arteriograms had normal thallium-201 myocardial perfusion scintigrams at rest. Two of the 20 patients with normal rest scintigrams developed perfusion defects on exercise associated with chest pain and positive exercise electrocardiograms. Five additional patients with normal rest and exercise thallium-201 scintigrams had positive exercise electrocardiograms. No patient had significant Q waves. The specificity and sensitivity of exercise thallium scintigrams and exercise electrocardiograms are shown in Table 3.

The sensitivity of thallium-201 myocardial perfusion scintigraphy and electrocardiography related to the number of coronary arteries with greater than 70 per cent stenosis is shown in Table 4. While each of the patients with triple vessel disease had positive exercise perfusion scintigrams and positive exercise electrocardiograms, the thallium-201 (rest or exercise) scintigam was more sensitive than the rest or exercise electrocardiogram in patients with single vessel disease (6 of 6 patients vs. 3 of 6 patients). There was a progressive increase in both positive exercise scintigrams and exercise electrocardiograms with the number of coronary arteries involved.

The correlation of perfusion defects on the rest or exercise thallium-201 study with the anatomical location of coronary artery stenosis greater than 70 per cent is presented in Table 5. Anterior, apical, or septal perfusion defects were present in 22 of the 24 patients with left anterior descending disease, inferior defects in 15 of the 16 patients with right coronary disease, and posterolateral defects in 11 of the 15 patients with circumflex disease. The correlation is similar when coronary stenosis greater than 50 per cent is considered significant.

### Discussion

**DETERMINANTS OF THALLIUM MYOCARDIAL DISTRIBUTION**

The initial distribution of thallium-201 in the myocardium is dependent on both coronary blood flow and cellular extraction (Strauss et al., 1975; Strauss and Pitt, 1977). Strauss et al. (1975) compared the regional myocardial distribution of thallium-201 with that of radioactive microspheres under conditions of normal flow, and partial and complete coronary occlusion; the data indicate that the major determinant of thallium-201 distribution is blood flow. The results of studies of extraction efficiency under various experimental conditions are conflicting (Costin and Zaret, 1976; Weich et al., 1977). Image defects in the rest thallium-201
scintigram generally represent myocardial infarction (Hamilton et al., 1977). In the resting non-ischaemic state, viable myocardial regions supplied by stenotic coronary arteries are usually adequately perfused in either an anterograde or retrograde fashion. Resting coronary blood flow and regional distribution were both normal in animals, despite coronary stenosis of 85 per cent in diameter (Gould et al., 1974). However, the ability to increase coronary flow in response to stress became progressively abnormal with coronary stenosis exceeding 45 per cent. In the present study, normal thallium-201 rest images were found in patients with 90 to 95 per cent coronary stenosis, unless prior infarction had occurred. Under stress, myocardial segments supplied by coronary arteries with 50 per cent or greater luminal narrowing became transiently ischaemic resulting in a perfusion defect that correlated well with the specific coronary artery which was stenosed.

SENSITIVITY AND SPECIFICITY OF PERFUSION SCINTIGRAPHY AND ELECTROCARDIOGRAPHY

Significant coronary artery stenosis may result in myocardial infarction, in myocardial ischaemia, or it may be silent. Therefore, the demonstration of infarction and/or ischaemia is considered evidence of significant coronary stenosis. Both abnormal Q waves in the resting electrocardiogram and exercise induced ST segment depression lack specificity and sensitivity (Horan et al., 1971; Borer et al., 1975; Fortuin and Weiss, 1977). The results of the present study show that the sensitivity of exercise induced scintigraphic abnormalities (81%) is higher than ST segment depression (58%) on the exercise electrocardiogram (P < 0.05), confirming recent studies evaluating these procedures in patients with myocardial ischaemia (Bailey et al., 1977; Ritchie et al., 1977a, b; Botvinick et al., 1978). Combined exercise thallium-201 scintigraphic and electrocardiographic evaluation was more sensitive than the exercise electrocardiogram alone (P < 0.01). Therefore the two procedures are complementary. Rest and exercise thallium-201 scintigraphy seem more sensitive in the detection of haemodynamically significant coronary artery disease than rest and exercise electrocardiography but because of the small number of patients studied this was not statistically significant (0.01 > P > 0.05). The specificity of thallium-201 exercise scintigraphy in this study was 90 per cent while the specificity of exercise electrocardiography was 65 per cent (P < 0.05). These results, similar to those of Ritchie et al. (1977a) and Botvinick et al. (1978), were obtained from a selected population; more experience is necessary before the specificity of thallium scintigraphy is definitely established.

FALSE NEGATIVE EXERCISE THALLIUM SCINTIGRAMS

Five patients with significant coronary stenosis exercised to the development of angina pectoris had false negative exercise thallium-201 scintigrams. Four had an old extensive myocardial infarction documented by Q waves 0.04 s or greater and an abnormal rest thallium-201 image. The absence of an increase in the rest image defect with exercise may be the result of the infarct concealing an adjacent region of exercise-induced ischaemia. The exercise electrocardiogram was negative in 3 of these 4 patients. While previous studies have suggested that in patients with severe triple vessel disease, global ischaemia may be produced by exercise and a focal perfusion defect may not appear (Pitt and Strauss, 1976), it is noteworthy that each of our patients with angiographically significant triple vessel disease had positive exercise thallium-201 scintigrams. Two of the 5 patients with false negative exercise scintigrams had single vessel disease and 3 had double vessel disease. It is important to remember that the coronary arteriogram reflects an anatomical state, whereas the myocardial perfusion scan reflects the functional regional status of myocardial perfusion. A direct relation between the two techniques does not always exist. Furthermore, the appearance of chest pain during exercise in the absence of ST segment depression and/or a myocardial perfusion defect does not indicate that the patients were in fact ischaemic and, therefore, that the above tests were true false negatives.

SCINTIGRAPHY AND CORONARY ARTERIOGRAPHY

The correlation of thallium perfusion defects at rest and/or exercise with angiographically significant coronary stenosis was higher for the left anterior descending and right coronary arteries than for the circumflex coronary artery. These results are similar to those reported by McLaughlin et al. (1977) though the correlation in the present study was slightly higher for circumflex artery disease.

ADVANTAGES OF 4-HOUR POST-EXERCISE STUDY

Our results with patients imaged 10 minutes after exercise and 4 hours later agree with those of Pohost et al. (1977) and Blood et al. (1977). Exercise induced perfusion defects were not apparent after 4 hours in patients with coronary stenosis without infarction. The images obtained 4 hours after exercise were similar to rest images obtained 1 week before the exercise study. This confirms that 2 separate studies 1 week apart are not necessary. In addition to the information being available the same day, the

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exercise and 4-hour post-exercise study technique requires only 1 dose of thallium-201 and, therefore, is less expensive and provides less radiation exposure.

CLINICAL IMPLICATIONS
Myocardial perfusion scintigraphy with thallium-201 is a safe, non-invasive diagnostic technique. The images are of good quality, and can be obtained with a conventional gamma scintillation camera. Thallium-201 scintigraphy represents an objective screening test for identifying significant coronary artery disease in patients with an atypical clinical history and a negative exercise electrocardiogram, and for confirming suspected myocardial infarction. This technique is helpful in assessing the presence or absence of coronary disease in asymptomatic patients with a positive exercise electrocardiogram (Zaret et al., 1973a; Caralis et al., 1977), and for evaluating the results of aortocoronary bypass surgery (Greenberg et al., 1977; Kostuk et al., 1977; Narahara et al., 1977; Ormand et al., 1977; Sbarbaro et al., 1977; Wainwright et al., 1977; Corne et al., 1979), pharmacological interventions (Salel et al., 1974), and modifications of risk factors for coronary artery disease. More experience with this technique is necessary before the specificity is established. We have found that the quantitative computer method employed in this study was of value in those cases of interobserver disagreement using non-processed analogue images and also increased the sensitivity in the interpretation of rest scintigrams. It is anticipated that when comparative studies of medical and surgical treatment are evaluated a more accurate estimate of regional myocardial perfusion will be available than with visual analysis of analogue images.

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References


Thallium scintigraphy

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