Myocardial Imaging with Thallium-201 at Rest and during Exercise

Comparison with Coronary Arteriography and Resting and Stress Electrocardiography

JAMES L. RITCHIE, M.D., GENE B. TROBAUGH, M.D., GLEN W. HAMILTON, M.D.,
K. LANCE GOULD, M.D., KENNETH A. NARAHARA, M.D., JOHN A. MURRAY, M.D.,
AND DAVID L. WILLIAMS, PH.D.

SUMMARY Myocardial imaging with intravenous thallium-201 (\(^{201}\)TI) was performed at rest and following maximal treadmill exercise in 101 patients with suspected coronary artery disease. Results were interpreted from Polaroid scintiphotos by three independent observers with complete interobserver agreement in 79%. Of 25 patients with no or insignificant coronary artery disease (< 50% diameter stenosis), one (4%) had a resting \(^{201}\)TI image defect, one (4%) had an exercise \(^{201}\)TI defect, none had an ECG Q wave, and four (16%) had exercise ST-segment depression. Among 76 patients with coronary artery disease (≥ 50% diameter stenosis), 58 (76%) had a defect on either the rest or exercise \(^{201}\)TI image. The proportion of patients with an exercise image defect (50/76, 66%) was greater than the proportion with exercise ST depression alone (34/76, 45%; P < 0.02). Overall, 69 of the 76 (91%) patients with coronary artery disease had either a positive rest or exercise myocardial image and/or a positive rest (ECG Q waves) or exercise (ST depression) electrocardiogram. This exceeded the proportion with only rest or exercise electrocardiographic abnormalities (50/76, 65%; P < 0.001).

We conclude that rest and exercise myocardial imaging with \(^{201}\)TI is easily accomplished with readily available imaging equipment. The image data enhanced the diagnostic sensitivity of stress electrocardiography, and provided spatial identification of the abnormal segment(s) of myocardium.

MYOCARDIAL IMAGING following the intravenous or intracoronary injection of radionuclides provides a useful clinical method for the detection of prior myocardial infarction\(^1\) and stress-induced regional myocardial ischemia.\(^2\) Of the various radiopharmaceuticals (tagged particles, \(^{40}\)K, \(^{82}\)Rb, and \(^{137}\)Cs) available, all have had significant limitations. The injection of tagged particles is strictly invasive; \(^{40}\)K and \(^{82}\)Rb provide relatively poor myocardial-to-background ratios, necessitate special whole body shielding for use with scintillation cameras,\(^2\)\(^5\) and have limited availability; myocardial uptake of \(^{137}\)Cs is not sufficiently rapid to detect transient myocardial ischemia induced by exercise stress.\(^7\)\(^8\) The recent cyclotron production of \(^{201}\)TI by Lebowitz et al.\(^9\)\(^10\) appears to overcome many of these limitations. Following intravenous injection at rest, myocardial \(^{201}\)TI uptake provides diagnostic quality images on currently available scintillation cameras using standard collimation. Myocardial uptake is sufficiently rapid that injection of the isotope during exercise allows detection of stress-induced myocardial ischemia.

This study addresses the question: does myocardial imaging at rest and following maximal treadmill stress enhance the diagnostic sensitivity of rest and stress electrocardiography. The image results are also correlated with findings at coronary arteriography.

Materials and Methods

Myocardial imaging was performed in 101 patients with known or suspected coronary artery disease; each patient had cardiac catheterization with selective coronary arteriography and ventriculography, clinical evaluation, and rest-stress electrocardiography. The patients represent an unselected consecutive series having catheterization when \(^{201}\)TI was available. Ninety-four patients were male, seven female; mean age was 50 (range 24 to 68). Patients who had had prolonged rest pain (pre-infarction like angina) were considered unsuitable for exercise testing and were not included in this series. The rest and exercise imaging was completed within 14 days of catheterization in all patients, and there was no evidence for progression of cardiac disease during this period. Patients studied for the investigation of valvular heart disease, cardiomyopathy, or evaluation following coronary artery surgery were excluded from this analysis. All patients were advised of the experimental nature of the study and gave informed consent.

Myocardial Imaging

Myocardial imaging was initially performed at rest. Following a five hour fast, 2 mCi of \(^{201}\)TI* was injected intravenously with the patient standing to minimize hepatic and gastric activity. Imaging was begun 20 min following isotope injection for the study performed at rest. For exercise imaging, the isotope was injected 60 sec prior to the termination of the treadmill test (estimated from a prior exercise test) and imaging begun 10 min following termination of exercise. Injection-to-imaging times were based on serial one minute studies following injection, which showed that maximal myocardial-to-background ratios occur 10 and 20 min post-injection for exercise and rest, respectively.\(^11\) An Ohio-Nuclear Series 100 scintillation camera was used for all studies. The camera was peaked with a \(^{201}\)TI point source by centering a full-width half-maximum window (25%) over

the photo peak of the mercury X-rays (approximately 80 KeV) with the collimator in place. A converging collimator* was used in the initial 40 patients and a high resolution, parallel hole collimator† in the subsequent 61 patients. Measured resolution of the two collimators at 80 KeV is similar. Occasional difficulty in precise patient repositioning between the rest and exercise study (secondary to depth magnification) led to exclusive use of the parallel hole collimator. Three hundred thousand count scintiphotos were obtained in the anterior, 45° left anterior oblique (LAO), and left lateral positions by rotation of the camera head over the supine patient to allow exact repositioning between the resting and exercise studies. A minimum of five days between the resting and exercise study was allowed to minimize residual radioactivity.

Analog images were recorded with a trilens Polaroid camera without additional contrast enhancement or computer processing. For the rest study, an image defect was defined as a discrete region of absent or nearly absent activity (estimated visually as greater than 50% diminished) when compared to a normal image. Image defects in the exercise study were defined as discrete, regional decreases in activity compared to the patients' own rest study. The anatomic location of a defect was determined from the LAO view (as previously described[1, 2]), in which the medial wedge represents the left anterior descending coronary distribution (anterior defect), the posterolateral wedge, the circumflex coronary distribution (a posterior defect), and the inferior wedge, the posterior descending coronary distribution (an inferior defect). Excepting defects at the apex, image abnormalities were not considered defects unless they were visualized in the LAO image (this view best separates the arterial distributions). Only absence of activity at the apex was considered an apical defect; diminished activity represents a normal variant corresponding to anatomic thinning of the apical myocardium.[3] Each set of rest-exercise images was read independently by three observers without other clinical or catheterization information, coded as normal or abnormal, and the location of abnormality recorded. Final readings reported represent total agreement (80/101, 79%) or a consensus opinion of two of three observers (21/101, 21%).

### Stress Testing

Electrocardiographic stress testing was performed twice in each patient; once during routine clinical evaluation and again for exercise imaging. In all cases, standardized graded treadmill exercise described by Bruce[4] was performed to a symptom limited maximum. The electrocardiogram was continuously monitored (modified V5 electrode) and interpreted as positive if 1 mm of flat or downsloping ST-segment depression was observed during or following exercise. The duration of exercise was expressed as functional aerobic impairment (FAI) calculated by comparison to age and sex matched controls.[4]

### Angiography

Coronary arteriography was performed using the Judkins technique and recorded on both 35 mm cine and large film. Coronary arteriograms were evaluated independently by two observers not aware of other clinical or image data, and the percent diameter stenosis of lesions and their location noted. If there was agreement between the two observers within the subgroups of 0–50%, 50–75%, 75–99%, and 100% for a given stenosis, then the average of the two readings was employed. In 14 patients in which there was disagreement, films were reviewed jointly with a third observer and a consensus reached.

### Results

Satisfactory myocardial images were obtained in all patients studied. Based on the combined resting and postexercise 201TI images, patients could be classified into four categories: normal/normal; normal/abnormal; abnormal/no change; and abnormal/with increased abnormality following exercise. Overall, 71 patients had normal images performed at rest; 40 of these remained normal; and 31 developed a discrete region of diminished activity (a perfusion defect) in the study performed after exercise (figs. 1 and 2). Thirty patients demonstrated perfusion defects in the

---

*Searle Radiographics Model #822017.
†Ohio-Nuclear Model #14518010.
study performed at rest. Nine of these showed no change following exercise and 21 developed additional and/or larger defects in the exercise study (fig. 3). For the purpose of this study, rest and exercise image studies were analyzed separately. That is, a patient was considered to have a rest defect whether or not a new defect was identified on the exercise study, and a patient was defined as having an exercise defect only if a new defect (one in addition to that present at rest) developed following exercise. Figures 2 and 3 (see below) illustrate the two types of exercise defects (normal/abnormal and abnormal/increased abnormality, respectively).

Figure 1 shows a patient with no coronary disease and normal images at rest and during exercise. The study injected during exercise was routinely of better quality than the resting study, with improved myocardial/background ratio and diminished hepatic activity when compared to the rest image. The right ventricle was routinely visualized on the exercise study but rarely seen on the rest study. Figure 2 illustrates a patient with coronary disease and a normal resting image. This patient had an isolated 85% left anterior descending coronary artery stenosis, had moderate impairment of exercise duration (FAI = 34%), and developed angina and 3 mm of ST-segment depression with exercise testing. Following exercise, there is reduced activity in the anterior myocardium, corresponding to the diseased left anterior descending coronary artery. Figure 3 demonstrates a patient with an abnormal resting image; following exercise there is increased abnormality in the same region. This patient had had a prior myocardial infarction by clinical history and enzyme elevations but had no ECG Q wave. Treadmill exercise duration was normal (FAI = 10%), and he developed neither angina nor ST-segment depression. The anterior apical defect anatomically corresponds best to the 100% occlusion of a large diagonal coronary artery; there were no image defects, however, in the posterior or inferior regions, both of which also had 100% coronary artery occlusions.

Of the entire group of 101 patients, 25 (25%) had either insignificant (less than 50% coronary stenosis) or no coronary artery disease. Seventy-six (75%) had coronary disease that could have hemodynamic significance with a 50% or greater coronary stenosis in at least one vessel. Twenty patients had single-vessel disease, 39 had two-vessel disease, and 17 had three-vessel disease. The percentage of patients with ECG Q
waves, exercise ST-segment depression, exercise treadmill induced angina, and abnormal resting or exercise 201TI images is shown in figure 4. In the 25 patients with no or insignificant coronary disease (left hand columns), three patients (12%) had exertional angina and four patients (16%) developed ST depression during exercise testing. None had ECG Q waves, one (4%) had a defect on the resting 201TI image, and one (4%) developed a 201TI image defect following exercise. Of the 76 patients with coronary artery disease (right hand columns, figure 4), 21 (28%) had ECG Q waves, 34 (45%) had exercise-induced ST depression, 48 (63%) developed angina during the exercise test, 29 (38%) had resting 201TI defects, and 50 (66%) developed a new or increased 201TI perfusion defect following exercise.

The relationship between exercise-induced ST depression and the exercise 201TI studies for all patients with significant coronary artery disease is shown in figure 5. Only those defects in the exercise 201TI image which were new or enlarged with exercise are included; resting defects that were unchanged after exercise were excluded. Among the 76 patients with coronary artery disease, 14 (18%) were normal with regard to both exercise ST-segment depression and exercise 201TI imaging. 12 (16%) had exercise ST depression and no new exercise image defects, 28 (37%) had abnormal exercise images and a normal exercise ST, and 22 (29%) had both exercise ST-segment depression and exercise 201TI image abnormalities. The proportion of patients having a new image defect with exercise (50/76, 66%) was greater than the proportion with exertional ST-segment depression (34/76, 45%; P < 0.02). *

Figure 6 illustrates the findings for both rest/exercise electrocardiography and rest/exercise 201TI images, as well as the combination of rest and exercise studies among the 76 patients with coronary artery disease. Studies performed at rest were the least sensitive predictors of coronary artery disease (left hand bars), those performed at exercise were more sensitive (middle bars), and the two combined were the most sensitive (right hand bars), such that 69 of 76 patients (91%) had at least one abnormality (i.e., either an ECG Q wave, exercise-induced ST-segment depression, or rest and/or exercise-induced 201TI image defects). This proportion of patients with any one of these abnormalities (69/76, 91%) was greater than that with only ECG evidence (Q wave or exercise ST depression) alone (50/76, 65%; P < 0.001). Thus, 201TI imaging and rest and exercise electrocardiography were supplemental such that the addition of myocardial imaging enhanced the diagnostic sensitivity of exercise electrocardiography.

Discussion

Resting and stress electrocardiography are useful predictors of coronary artery disease. Unfortunately, neither the
resting Q wave nor exertional ST depression are specific for coronary artery disease,\textsuperscript{15, 16} and both lack sensitivity.\textsuperscript{15, 17} Zaret and Strauss et al. introduced the concept of exercise myocardial imaging with \textsuperscript{40}K to detect regions of exercise-induced myocardial ischemia. Their studies with \textsuperscript{43}K\textsuperscript{1} and subsequent work by Martin et al.\textsuperscript{9} and Berman et al.\textsuperscript{10} with \textsuperscript{81}Rb demonstrated that imaging was a more sensitive predictor of coronary artery disease than exertional ST-segment depression.

The studies reported here document the usefulness of \textsuperscript{201}TI imaging for the detection of exercise-induced myocardial ischemia. All but two patients studied with resting or exercise \textsuperscript{201}TI image defects had coronary disease (\textgeq 50% stenosis). One of these patients had typical angina, exercise ST-segment depression, entire normal coronary arteries, and an exercise-induced image defect. A second patient had atypical chest pain, no exercise ST depression, and an inferior image defect at rest which was unchanged with exercise. His coronary angiogram showed only 40% occlusion of the distal left anterior descending coronary artery. The latter patient, although counted here as a false positive, may have had an old myocardial infarction detected only by the \textsuperscript{201}TI image. The former patient is a definite false positive although he may represent a patient with normal coronary arteries and "angina." Seventeen patients in this study had angiographic evidence of coronary artery disease but negative rest and exercise myocardial images (i.e., false negative image studies); the overall sensitivity of the test was 76%:

\[
\text{true positives (58)}
\]
\[
\text{true positives (58) plus false negatives (18)}
\]

In one patient there was an isolated 80% stenosis of a diminutive right coronary artery, and in another there was an isolated stenosis of a small, distal circumflex coronary artery; the failure to detect perfusion defects in these two patients is not unexpected from the small mass of myocardial tissue supplied by these vessels. Fifteen patients had no \textsuperscript{201}TI image abnormalities in spite of significant stenosis in at least one major coronary artery. There were no other identifiable features which separated this group of false negative studies from patients who developed image defects. Mean duration of exercise, the proportion of patients with exercise ST depression or exercise angina, and the proportions with one, two, or three vessel coronary artery disease were not different between the two groups. The 92% specificity of \textsuperscript{201}TI imaging for coronary artery disease is high:

\[
\text{true negatives (23)}
\]
\[
\text{true negatives (23) and false positives (2)}
\]

However, it may not be generally applicable in that it reflects a relatively small number of "normals" in a predominantly male population.

Myocardial uptake of monovalent cations is a well recognized phenomenon;\textsuperscript{7, 14} the mechanism of \textsuperscript{201}TI myocardial uptake resembles that of potassium. Both have a similar ionic crystal radius size, and both activate Na-K adenosine triphosphatase.\textsuperscript{19, 20} Lebowitz et al.\textsuperscript{9, 10} and Strauss et al.\textsuperscript{18} have shown that the blood clearance and myocardial uptake of \textsuperscript{201}TI are similar to that for \textsuperscript{43}K and \textsuperscript{81}Rb. The whole body and organ specific radiation burden is approximately equal for \textsuperscript{201}TI, \textsuperscript{81}Rb, and \textsuperscript{43}K.\textsuperscript{21} Radiation dose for \textsuperscript{201}TI per mCi is 0.24 rads whole body, 0.17 rads heart, 0.39 rads kidneys, and 0.30 rads testes.\textsuperscript{21}

Most importantly, image quality with \textsuperscript{201}TI is improved compared to prior agents. The in vivo myocardial/background ratio is substantially better than that for \textsuperscript{43}K, and standard scintiphotographs require no contrast enhancement to provide images of diagnostic quality.\textsuperscript{6, 22} The predominately low energy gamma emissions of \textsuperscript{201}TI (approximately 10% abundance at 135 KeV and 5% at 167 KeV) and mercury X-rays (98% abundance at 69–83 KeV) are quite suitable for imaging with standard scintillation cameras without the special shielding modifications required for \textsuperscript{81}Rb or \textsuperscript{43}K.

Studies from this and other laboratories have shown that image defects present at rest (with intravenous \textsuperscript{43}K, \textsuperscript{81}Rb, \textsuperscript{201}TI, \textsuperscript{125}Cs, or intracoronary MAA) represent prior myocar-
The resting images do not, however, detect hemodynamically significant coronary stenoses unassociated with infarction. The experimental studies of Gould et al.28, 29 showed that resting coronary blood flow and regional flow distribution remained normal in spite of severe coronary stenosis (> 85% diameter). During periods of increased coronary flow induced by exercise or pharmacologic vasodilators, stenoses exceeding 50% produced progressive blood flow and regional distribution abnormalities. During stress, coronary blood flow to such regions fails to increase appropriately compared to normal myocardium, and blood distribution studies with radioactive particles demonstrate a defect in the affected region.28, 29 A similar mechanism is presumed to apply in the development of exertional image defects with \( ^{201}\text{Tl} \) and is supported by the work of Strauss et al.,30 who showed experimentally that the myocardial distribution of \( ^{201}\text{Tl} \) paralleled blood flow under conditions of normal or acutely decreased flow.

It should be stressed that the results of this study apply principally to the detection of coronary artery disease per se, rather than the detection of individually stenotic coronary arteries. Although the location of an image defect corresponded to that of a stenotic artery in all patients with single-vessel disease, most patients in this series had two- or three-vessel disease. In these patients, the image defect was always associated with a corresponding coronary artery stenosis; however, in many cases (such as that in figure 3), other high-grade lesions were present angiographically, but image defects did not develop in these regions. Possible explanations include 1) the development of ischemia in only one of several potentially ischemic zones for a given level of exercise; 2) the variable contribution of collateral flow; 3) erroneous angiographic interpretation; and 4) global ischemia in which only the most abnormal area appears as an image defect by visual analysis.

Overall, the present study supports the promise of \( ^{201}\text{Tl} \) rest and exercise imaging in the detection of regional myocardial ischemia, and documents improved sensitivity in the detection of coronary artery disease when the procedure is combined with stress electrocardiography.

References


2. Hamilton GW, Ritchie JL, Allen D, Lapin E, Murray J: Myocardial perfusion imaging with \( ^{99m}\text{Tc} \) or \( ^{111m}\text{In} \) macroaggregated albumin: Correlation of the perfusion image with clinical, angiographic, surgical, and histologic findings. Am Heart J 89: 708, 1975


21. Feller PA, Sodd VJ: Dosimetry of four heart-imaging radionuclides; \( ^{99m}\text{Tc}, ^{111m}\text{In}, ^{85}\text{Kr}, \) and \( ^{201}\text{Tl} \). J Nucl Med 16: 1070, 1975


Myocardial imaging with thallium-201 at rest and during exercise. Comparison with coronary arteriography and resting and stress electrocardiography.

J L Ritchie, G B Trobaugh, G W Hamilton, K L Gould, K A Narahara, J A Murray and D L Williams

Circulation. 1977;56:66-71
doi: 10.1161/01.CIR.56.1.66

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1977 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/56/1/66

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/