Noninvasive Detection of Regional Myocardial Ischemia Using Rubidium-81 and the Scintillation Camera

Comparison with Stress Electrocardiography in Patients with Arteriographically Documented Coronary Stenosis

By Daniel S. Berman, M.D., Antone F. Salel, M.D., Gerald L. DeNardo, M.D., and Dean T. Mason, M.D.

SUMMARY
The sensitivity of rest and stress myocardial perfusion studies using scintillation camera imaging of intravenously administered rubidium-81 (81Rb) in the detection of myocardial ischemia was compared to that of stress electrocardiography by relating results in 40 patients to the degree of stenosis delineated by coronary arteriography. Of 33 patients with greater than 75% stenosis of at least one of the three major coronary vessels (significant stenosis), rest and stress 81Rb imaging detected ventricular ischemia in 29 (88%), whereas simultaneous stress electrocardiography was positive (1 mm or greater horizontal ST-segment depression) in only 19 (58%) of the same patients. Five of the 29 patients who developed stress-induced scintigraphic evidence of ischemia did not develop angina or a positive electrocardiogram with stress. In 31 of the 33 patients with significant coronary stenosis, either the stress scintigram or the stress electrocardiogram was positive. In seven patients with less than 50% narrowing of a major coronary vessel on coronary arteriography, the stress scintigrams were negative, whereas the stress electrocardiograms were positive in the two of these patients with the syndrome of angina with normal coronary arteriograms. It is concluded that high resolution images of the myocardium can be obtained with 81Rb using the scintillation camera with special shielding, and that rest and stress 81Rb scintigraphy appears to provide greater sensitivity and specificity when compared to stress electrocardiography in the noninvasive identification of significant coronary stenosis.

IN THE EVALUATION of coronary artery disease, the treadmill electrocardiogram has proven to be a useful but imprecise indicator of myocardial ischemia.† Although radionuclidic imaging at rest is capable of detecting most myocardial infarctions,‡ it is not sensitive for the detection of coronary disease without infarction.§ Recently, a technique has been described which combines scintigraphy with treadmill stress testing using either potassium-43 (43K) or rubidium-81 (81Rb) and the rectilinear scanner.¶ This method is noninvasive and avoids the complications of coronary arteriography. Although the specificity for coronary disease of this combined rest and exercise technique has been evaluated,‖ the sensitivity has not been determined previously by correlation with coronary arteriographic findings in nonselected patients.

This report provides an evaluation of myocardial imaging at rest and after stress using 81Rb and a scintillation camera in the detection of significant coronary stenosis as determined by coronary arteriography. In addition, this study compares the sensitivity of 81Rb myocardial imaging with that of stress electrocardiography.

Materials and Methods

Patients
Radionuclidic myocardial imaging was performed on 40 adults with known or suspected coronary artery disease; each patient had cardiac catheterization with selective coronary arteriography. Of the 40 patients, 17 had prior myocardial infarctions, and the other 23 had chest pain suggestive of angina pectoris. In 32 patients, scintigraphy was performed within two days of the cardiac catheterization. Of the remaining patients, five had scintigraphic evaluation within one month and three within two months of the cardiac catheterization. There was no clinical or electrocardiographic evidence of progression of coronary disease between the radionuclidic and angiographic analyses.
Radionuclidic Studies

(1) Rest and Stress Scintigraphy

Each of the 40 patients had a radionuclidic study performed at rest and after maximal cardiac stress. Because of the 4.6 hour physical half life of $^{81}$Rb, only a 48-hour interval between the two parts of the study was required to allow for radionuclidic decay. The patients were maintained fasting for ten hours, and the radiopharmaceutical was administered to the patient, who was in the upright position in order to minimize gastric and hepatic radioactivity. For each portion of the study, 4 mCi of $^{81}$Rb chloride was injected into a peripheral vein. The $^{81}$Rb was obtained from a commercial supplier (Medi-Physics, Inc.) and contained a substantial amount of contaminant rubidium-82m ($^{82m}$Rb). The estimated whole body absorbed radiation dose with the agent was 0.22 rads/mCi.

Imaging was performed using a scintillation camera (Searle Radiographics Pho-Gamma HP) equipped with a pinhole collimator and a specially constructed lead shield (fig. 1). The additional shield provided two inches of lead to supplement the shielding provided by the standard pinhole collimator. A tungsten insert with an aperture of nine millimeters in diameter was used with the pinhole collimator.

Beginning two minutes after injection, images in the anterior, left anterior oblique, and left lateral positions, and consisting of 200,000 scintigraphic counts, were exposed on Polaroid film first employing the 190 KeV peak of krypton-81m ($^{81m}$Kr) and then the 511 KeV peak of $^{81}$Rb. A 20% window was used for all images. The time required for each image varied from three minutes with the 190 KeV peak to ten minutes with the 511 KeV peak.

Prior to starting the stress portion of the study, a two inch teflon catheter was placed into an antecubital vein. The radionuclide was injected after the development of chest pain, maximal predicted heart rate, or severe fatigue. The stress procedure was continued at maximal intensity for an additional 30 seconds after injection. The four lead electrocardiogram was continuously monitored from the beginning of the stress test to the end of the imaging procedure.

Neither the patient's clinical state nor his angiographic findings were known to the observer interpreting the scintigrams. If both rest and stress studies demonstrated homogeneous distribution of radioactivity, they were interpreted as normal. Studies which demonstrated decreased radioactivity in regions which normally have homogeneous uptake were considered abnormal. Studies in which a focal defect was present at rest were interpreted as suggestive of infarction. When a focal area of decreased activity was demonstrated after stress that was either not present or less apparent on the resting study, the studies were considered indicative of regional ischemia.

(2) Technical Considerations

In order to evaluate the need for special lead shielding when using $^{81}$Rb and the scintillation camera, myocardial imaging at rest was performed in one patient both with and without the additional shielding. Furthermore, the adequacy of the special lead shielding was assessed by determining count rates both with and without the lead shielding, using a point source containing 0.73 mCi of $^{81}$Rb. The point source was counted for ten seconds at each 2 cm interval along a line parallel to the detector at the height of the pinhole, and at a distance of three inches from the front on the pinhole collimator. The fraction of the incident gamma emissions effectively shielded was determined by dividing the average count rate outside the field of view to that within the field of view of the pinhole collimator.

Stress Electrocardiography

Electrocardiographic stress testing was performed immediately prior to the injection of radionuclide for the stress phase of the radionuclidic studies. In 30 patients the stress test consisted of treadmill exercise using the graded Bruce protocol.7 Exercise was carried to the point of maximal predicted heart rate, development of angina pectoris, or severe fatigue. In the remaining ten patients, transvenous cardiac pacing was performed by staged increases in heart rate.8 Pacing was continued to maximal heart rate or to onset of angina pectoris. For both treadmill and pacing stress tests, a four lead electrocardiographic monitoring system was employed (leads I, II, aVf and V5). Stress electrocardiography was interpreted as positive if there was development of persistent flat or down-sloping ST-segment depression of 1 mm (0.1 mV) or greater during or immediately following exercise in a lead which had an isoelectric ST segment in the control tracing.

 Coronary Arteriography

During complete right and left heart catheterization, selective coronary arteriography was performed in multiple projections employing the Judkins technique. Exposures were made on 35 mm film taken at 64 frames/sec using the Philips 9 and 5 inch image intensifier system. The coronary vessels were visualized with 2–10 cc of Renografin-76% containing sodium and meglumine diatrizoates. Disease of the coronary circulation was evaluated by inspection of the arteriograms for luminal narrowing. Greater than 75% stenosis of one or more of the three major coronary arteries was interpreted to be indicative of significant hemodynamic obstruction.9, 10

Results

Coronary Arteriography

Thirty-three of the 40 patients had greater than 75% stenosis of at least one of the three major cor-
SCINTIGRAPHIC DETECTION OF ISCHEMIA

Coronary arteries. Stenosis greater than 75% was demonstrated in all three of the major coronary arteries in 14 patients, in two major arteries in seven patients, and in one major coronary artery in 12 patients. The remaining seven of the 40 patients had either normal coronary arteriograms or less than 50% narrowing of a major coronary artery. None of the patients demonstrated lesions between 50 and 75% without at least one other major vessel having greater than 75% stenosis.

Stress Electrocardiography (table 1)

Nineteen of the 33 patients with significant coronary artery stenosis had stress electrocardiographic evidence of ischemia (58%). False negative stress electrocardiograms were most common in patients with single vessel disease in whom the electrocardiographic test was positive in five of 12 (42%). Stress electrocardiography was negative in five of the seven patients with either normal coronary arteriograms or lesions of less than 50% stenosis, but was positive in the remaining two patients. These two patients had the syndrome of angina pectoris with normal coronary arteriograms.

Rest and Stress Scintigraphy (table 1)

Twenty nine (88%) of the 33 patients with arteriographic lesions of greater than 75% in at least one major coronary artery demonstrated evidence of ischemia on the stress scintigrams. This frequency of positive scintigraphic studies was significantly greater than that with stress electrocardiography (P < 0.01). Four patients with significant stenosis on coronary arteriograms had no radionuclidic evidence of ischemia. These four false negative studies included the following: (1) a patient with severe chronic obstructive pulmonary disease whose dyspnea limited treadmill exercise so that no electrocardiographic evidence of ischemia occurred; (2) a second patient in whom leg fatigue caused cessation of exercise before maximal predicted heart rate, pain or positive electrocardiogram was achieved; (3) one patient with significant disease of two vessels but no disease in the left anterior descending coronary artery; and (4) one patient with 75% stenosis of the left anterior descending coronary artery. Of the seven patients without significant stenosis of coronary arteries by arteriography, none of the rest or exercise scintigrams was positive.

A normal $^{81}$Rb image obtained with the shielded scintillation camera is shown in figure 2. Of the cardiac structures, the left ventricular myocardium was visualized best due to its relatively large mass and blood flow. On the anterior view, the apex, inferior wall, and lateral wall were well delineated. On the left anterior oblique (LAO) view, the left ventricle was seen from the apex, optimally displaying the interventricular septum and the posterior wall. In most cases the faint outline of the right ventricular wall was also visualized in the LAO view. The left lateral view best defined the inferior left ventricular wall.

Examples of patterns considered indicative of

### Table 1

<table>
<thead>
<tr>
<th>Coronary arteriography</th>
<th>Significant stenosis</th>
<th>No significant stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest &amp; exercise</td>
<td>35 patients</td>
<td>7 patients</td>
</tr>
<tr>
<td>Rb-$^{81}$ Scintigraphy</td>
<td></td>
<td></td>
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<td>0</td>
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<tr>
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<td>7</td>
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<tr>
<td>Stress electrocardiography</td>
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<td></td>
</tr>
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<td>2</td>
</tr>
<tr>
<td>Negative</td>
<td>14</td>
<td>5</td>
</tr>
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</table>

*Circulation, Volume 52, October 1975*
Scintigraphic images using the 511 KeV peak obtained at rest (A,C) and after exercise (B,D) in a patient with old posterior myocardial infarction and left anterior descending coronary artery (LAD) ischemia. The prominent posterior defect on the LAO both at rest (C) and after exercise (D) corresponds to the previous myocardial infarction, the striking defect in the apex after exercise (B) and not at rest (A) corresponds to a region of ischemia. Coronary arteriography revealed occluded right coronary and left circumflex coronary arteries and a 90% stenosis of the LAD.

Ischemia on comparative rest and exercise $^{81}$Rb scintigraphic images are shown in figures 3 and 4. The patient in figure 3 exhibited two classic patterns; first, a prominent defect was seen posteriorly both at rest and after exercise without change corresponding to a well documented posterior myocardial infarction associated with occluded right and circumflex coronary arteries; and, second, a defect is seen in the apex after exercise that is not seen at rest. The latter defect is indicative of ischemia in the distribution of the left anterior descending coronary artery and correlated with 90% proximal stenosis of this vessel. The patient in figure 4 demonstrates two additional points; first, ischemia is demonstrated by a normal resting scintigram and an abnormal exercise image with a defect in the apex corresponding to a 95% stenosis of the left anterior descending coronary artery; and, second, the value of the technique is demonstrated by postoperative exercise scintigraphy in which the perfusion pattern had returned to normal, thereby objectively documenting the efficacy of surgical myocardial revascularization in this patient.

Five patients with significant coronary stenosis on
selective arteriography and normal stress electrocardiograms were of interest. In these five patients, exercise images with \(^8\)Rb demonstrated defects that were either not present or less marked on resting images: the pattern of worsening of perfusion with exercise (fig. 5). In addition to negative stress electrocardiography, each of these patients was without chest pain induced during the stress test. The patient in figure 5 had an old diaphragmatic myocardial infarction. Resting scintigrams revealed decreased activity corresponding to previous diaphragmatic myocardial infarction. After exercise there was distinct worsening of this defect and appearance of a new defect in the apex. Arteriography revealed multiple lesions of greater than 75% in the right coronary artery, a 90% lesion of the left circumflex coronary artery, a 50% lesion of the left anterior descending coronary artery and a 90% stenosis of the left diagonal branch. Thus, significant arteriographic lesions were associated with positive scintigraphic evidence of ischemia in the absence of exercise-induced ECG abnormality or chest pain.

The combination of scintigraphy with stress electrocardiography was more sensitive in detecting coronary artery stenosis than either procedure alone. In the 33 patients with greater than 75% stenosis of at least one of the three major coronary arteries, either scintigraphy or stress electrocardiography was positive in 31 (94%), whereas scintigraphy alone was positive in 88% and stress electrocardiography alone was positive in 58%.

Technical Considerations in \(^8\)Rb Scintillation Camera Imaging

Additional lead shielding was required for scintillation camera imaging with \(^8\)Rb because of the abundant high energy gamma emissions from the \(^8\)Rb and the contaminant \(^3m\)Rb. Without the special shield image resolution was inadequate, whereas with the shield images of diagnostic quality were obtained in all patients (fig. 6).

The need for and adequacy of the additional shielding were also verified by the results of the point source experiment. Without the shield, when the source was outside the field of view of the pinhole, the count rate was reduced by only 70% (190 KeV peak) or 50% (511 KeV peak) of the rate obtained with the source within the field of view. In contrast, with the special shielding, when the source was outside the field of view the count rate was reduced by 99.5% (190 KeV peak) and 99% (511 KeV peak). This indicated that 99% or greater of the incident gamma emissions outside of the pinhole field of view were absorbed or sufficiently attenuated by the shield so that they were not counted within the 20% energy window. Thus the degree of shielding provided by additional lead was adequate for the imaging studies.

Prominent differences in the image characteristics were noted between the images taken with the 511 KeV photon peak and with the 190 KeV photon peak (fig. 7). Lung radioactivity was greater when the 190 KeV photon peak of \(^8\)mKr was accepted than when the 511 KeV photon peak of \(^8\)Rb was accepted due to relatively greater concentration of the \(^8\)mKr gas in the lungs. When the 190 KeV photon peak was used, in-

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Figure 5

Scintigraphic images using the 511 KeV peak obtained at rest (A,C) and after exercise (B,D) in a patient with old diaphragmatic myocardial infarction. LAO resting scintigram (C) reveals decreased activity in the posterior-inferior left ventricular wall corresponding to the previous myocardial infarction. Exercise scintigrams (B,D) reveal evidence of ischemia with worsening of the posterior-inferior defect (D) and appearance of a new apical defect (B). During exercise limited by severe fatigue there was no electrocardiographic evidence of ischemia, and the patient did not develop chest pain.

Figure 6

Anterior scintigraphic images obtained at rest in a patient with previous anterior myocardial infarction with (A,B) and without the special shield (C,D) using both the 190 and 511 KeV photon peaks.
creased pulmonary radioactivity caused a decrease in the heart-to-lung ratio and impaired myocardial resolution. Superior resolution of both the normal myocardium and defects attributed to ischemia or infarction was consistently observed throughout the study group when the 511 KeV photon peak was accepted.

Discussion

It has been known for more than two decades that monovalent cations concentrate in normal myocardium.\textsuperscript{11,\textsuperscript{12}} Recently, this knowledge has been used to develop myocardial imaging techniques which use radioactive cesium, potassium or rubidium. Although these techniques have made it possible to detect myocardial infarction,\textsuperscript{5} studies performed at rest have not been useful for the assessment of ischemia.\textsuperscript{3} The inability of the resting studies to detect significant coronary lesions in the absence of infarction occurs because resting blood flow is normal in coronary arteries with up to 85% stenosis.\textsuperscript{13,\textsuperscript{14}} Recent development by Zaret, Strauss and associates\textsuperscript{6-8} of radionuclidic myocardial imaging both at rest and after exercise has led to its application in the evaluation of patients with coronary artery disease without infarction. The rest and exercise technique requires that the radioactive isotope be distributed in the myocardium during the time of exercise-induced ischemia. Either potassium-43 or rubidium-81 can be used because they are rapidly cleared from the blood by the myocardium,\textsuperscript{11} but radioisotopes of cesium, although valuable for imaging at rest, are not suited to the rest and exercise approach because of their slow blood clearance.\textsuperscript{11,\textsuperscript{16}}

Our results demonstrate that rest and stress scintigraphy with \textsuperscript{81}Rb and the scintillation camera is more sensitive in the detection of significant coronary stenosis than the maximal stress electrocardiogram (table 1). The stress electrocardiogram was positive in only 58% of patients with significant arteriographic lesions, whereas the exercise scintigram was positive in 88% of these patients. Our over-all sensitivity for the stress electrocardiogram, higher sensitivity in patients with three vessel disease and lower sensitivity in patients with single vessel disease, is in accord with both the results of clinical stress testing in our cardiovascular laboratories\textsuperscript{16} and the results of others.\textsuperscript{17,\textsuperscript{18}}

Five patients with arteriographic evidence of significant coronary stenosis demonstrated radionuclidic evidence of ischemia with stress, although they had neither chest pain nor positive stress electrocardiograms (fig. 5). These findings suggest that the scintigraphic technique is more sensitive in the detection of ischemia than either symptoms or standard four lead electrocardiographic maximal stress testing.

Zaret and associates have demonstrated that combined rest and exercise \textsuperscript{43}K scintigraphy is positive in a high percentage of patients who have angina and stress electrocardiograms suggestive of ischemia.\textsuperscript{3} In addition, by studying a group of patients with positive stress electrocardiograms associated with arteriographically normal coronary arteries, these investigators have demonstrated that rest and exercise scintigraphy has greater specificity than stress electrocardiography in the detection of coronary artery disease. The present study establishes the sensitivity of stress scintigraphy since it included patients undergoing coronary arteriography irrespective of the results of stress electrocardiography or of the presence of chest pain, whereas in the previous reports patients with scintigraphic evidence of ischemia had either chest pain or electrocardiographic evidence of myocardial ischemia or both.\textsuperscript{19}

The findings in the two patients with the syndrome of angina pectoris and normal coronary arteriograms are of special interest and support the observations of Zaret and co-workers.\textsuperscript{6} In these two patients, rest and exercise scintigraphy showed no evidence of regional myocardial ischemia, whereas the stress electrocardiogram revealed 1 mm horizontal ST-segment depression in both. These findings support the concept that this condition is due to a diffuse metabolic defect or small vessel disease which produces global rather than segmental ischemia.\textsuperscript{20} Neither test should be considered falsely positive or falsely negative in

\textbf{Figure 7}

Anterior scintigraphic images obtained with the 190 KeV photon peak (A,C) and the 511 KeV photon peak (B,D) in a patient with significant three vessel disease on coronary arteriography. Exercise images (C,D) reveal a defect in the region of the apex that is not seen at rest (A,B). Note that the lung background is lower and the defect is more clearly defined with the 511 KeV peak (B,D) compared with the 190 KeV peak (A,C).
this condition, since the positive stress electrocardiogram indicates ischemia, and the negative stress scintigram signifies the absence of segmental ischemic disease.

Previous work with combined rest and exercise scintigraphy has generally been performed with the rectilinear scanner. Our results demonstrate that high resolution images can be obtained with \(^{81}\text{Rb}\) and the scintillation camera. The scintillation camera offers the advantage that images are obtained without distortion of the scintigraphic data due to contrast enhancement, which is necessary when myocardial studies are performed with the rectilinear scanner. The need for contrast enhancement with the rectilinear scanning technique is a particularly important disadvantage when studies must be performed at separate times and compared to one another as is required by rest and exercise myocardial scanning. The possibility of introducing artifactual defects with the rectilinear scanner through slight variations in scanning technique has been documented. Data collection with the scintillation camera on the other hand is performed without contrast enhancement, and thus is less subject to technical variation between studies performed at different times. The other chief advantage of the scintillation camera is the ease with which radionuclidic data obtained with the camera can be recorded by a special purpose computer for quantitative analysis. Thus the demonstration of high resolution myocardial imaging with \(^{81}\text{Rb}\) on the scintillation camera is of significant importance both for technical reasons and for computer applications.

Special lead shielding was required for camera imaging with commercially available \(^{81}\text{Rb}\) due principally to the presence of contaminant \(^{85}\text{Kr}\) with its abundant high energy gamma emissions (fig. 6); its gamma emissions include 511 KeV (66%), 554 KeV (66%), 619 KeV (41%), 777 KeV (83%), 1317 KeV (26%), and other photons. Gamma rays of these energies readily penetrate the lead shielding of the standard pinhole collimator used with the scintillation camera. The two inches of lead supplied by the specially constructed lead shield effectively reduced this collimator penetration.

In summary, rest and stress scintigraphy using \(^{81}\text{Rb}\) and the scintillation camera enhanced both the sensitivity and the specificity of stress electrocardiography in the noninvasive detection of significant coronary artery stenosis. Combined electrocardiographic and scintigraphic evaluation was more sensitive than either alone. Since stress electrocardiography is widely used as a screening test for coronary artery disease and since the radiation dose from the \(^{81}\text{Rb}\) studies is not great, there is little additional morbidity when the studies are combined.

Combined scintigraphic and electrocardiographic rest and exercise evaluations have many clinical applications. Our results demonstrate the validity of this approach as a noninvasive screening test for significant coronary stenosis. In a select group of patients in whom coronary disease is unlikely, negative rest and exercise scintigraphy combined with negative stress electrocardiography may provide sufficient evidence of the absence of coronary disease that cardiac catheterization would not be necessary. The study is also valuable in patients with arteriographic lesions of questionable hemodynamic significance. In these patients, the perfusion of the area in question after exercise when compared to rest offers an objective assessment of the functional significance of the coronary narrowing. A further group in whom we and others have already found the technique to be helpful are patients who undergo coronary bypass surgery (fig. 4). The comparison of rest and exercise scintigraphy after myocardial revascularization with the preoperative scintigraphic evaluation affords objective evidence of the efficacy of bypass surgery. Over a larger time span, serial rest and exercise studies can be used to evaluate the effects of long term multiple risk factor interventions in patients with chronic coronary disease. We have recently employed the technique as a means of assessing pharmacologic intervention by studying patients both before and after the administration of a beta blocking agent.

Finally, the scintillation camera makes quantitative evaluation possible by means of a digital computer. The decay of \(^{81}\text{Rb}\) to the noble gas, \(^{85}\text{Kr}\), has been used with a computer for the quantification of splenic blood flow through application of a variation of standard gas washout techniques and offers promise for measurement of regional myocardial blood flow with the specially shielded scintillation camera. Thus quantitative measurement of regional myocardial blood flow can be achieved with the scintigraphic data accumulated by the method formulated in this report.

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