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EVALUATION OF ^{201}THALLIUM SCANNING FOR DETECTION OF LATENT CORONARY ARTERY DISEASE

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EVALUATION OF ^{201}THALLIUM SCANNING FOR DETECTION OF LATENT CORONARY ARTERY DISEASE

Background

The use of radiothallium in nuclear medicine was first suggested by Kawana et. al. (1). The organ distribution (2) and neurophysiologic function (3) of thallium is similar to potassium. The reason for this is believed to result from the hydrated ionic radius of Tl^+ which is similar to K^+. This radius is believed to be the property that determines passive penetration through a membrane.

Potassium has been used for a number of years to estimate coronary blood flow because of the high extraction ratio of potassium by myocardial tissue. An extraction ratio is the fraction of the material removed from the blood in a single passage through tissue. Potassium has an extraction ratio of about 70%. The absolute or relative uptake of potassium or an analog of potassium indicates tissue perfusion. The isotopes of potassium that have been used, ^{43}K and ^{42}K have the disadvantage of short half lives, 22 and 12 hours respectively, and relatively high photon energy, 0.38 and 0.6 MeV for ^{43}K and 1.52 MeV for ^{42}K. ^{201}Thallium has a better half life, 73 hours, and good photon energies, 69-83 keV, which has renewed interest in myocardial imaging. ^{201}Thallium is a cyclotron-produced radionuclide which has been approved by the FDA for use in humans on a routine basis. The radiation exposure from ^{201}Tl administration is given in Table I (4).

Objective

The objective of this study was to investigate the use of ^{201}Thallium imaging as a noninvasive method to accurately screen shuttle passengers for latent coronary artery disease. It is anticipated that such a test when combined with other noninvasive tests will result in an acceptably low false negative rate and a reasonably low false positive incidence allowing it to be used during preflight testing of crew members and passengers.

<u>Methods</u>

This study was to evaluate the radionuclide procedure, hereafter called thallium image, scan or study, with the conventional invasive and noninvasive techniques that are routinely performed for patients with known or suspected coronary artery or myocardial disease.

All radionuclide procedures were performed using an Anger type camera with a high resolution collimator. A minimum of 200,000 counts were collected for each image using a 20% window centered on the 69-83 keV x-rays. Three views were routinely taken, anterior, 45^0 left anterior oblique and left lateral. For the images obtained following injection with the patient at rest, the testing was begun 10 minutes after injection. Injections of ^{201}Tl during exercise were made at a point near the termination of the treadmill procedure as determined by either the appearance of ST segment changes on the electrocardiogram consistant with subendocardial ischemia, the appearance of angina-like chest pain in the patient or fatigue in the patient which required cessation of the test.

The severity of heart disease was based on the medical history, physical exam, exercise electrocardiograms, chest x-rays and the coronary arteriogram.

The first part of this study (A) attempted to determine the sensitivity of ^{201}Tl imaging to detect damaged heart muscle. Thirty patients who were seen by the Cardiovascular Unit at Methodist Hospital because of suspected coronary disease received a resting thallium study, <u>i.e.</u>, the ^{201}Tl was injected with the patient at rest.

The second part of the study (B) evaluated the ability of ^{201}Tl imaging to detect ischemic heart disease. Twenty-eight patients who were seen by the Cardiovascular Unit at Methodist Hospital received a stress ^{201}Tl study. Stress was achieved by either a treadmill exercise or a right ventricle/atrial electrical pacing at the time of heart catherization. Exercise patients were continously monitored with a 12 lead EKG while heart rate and blood pressure were taken periodically during and after the exercise period. Approximately 30-60 seconds before exercise was stopped or at the time of pacing 1.5-2.0 mCi of ^{201}Tl was injected via a previously placed heparin-lock. Five minutes post injection imaging was begun and three views of the heart were taken. Four to six hours post injection the same three views were retaken. At this time the ^{201}Tl has had time to redistribute and the image obtained has been reported to be equivalent to a resting study (4,5).

All images in this part of the study were obtained using newer equipment with computer image enhancement (Elscint-CE-1-7, 37 PM tube gamma camera and Elscint Dycomette Display Processor). This equipment, which was designed for optimal performance at low energy gamma rays such as ^{201}Tl, has significantly improved resolution compared to the equipment used in part A of this report. The imaging technique was otherwise the same.

Informed consent was obtained from all patients. This study was approved by the Baylor Institutional Review Board for Human Research, The Methodist Hospital Institutional Review Board for Human Research and the Radioisotope Committees of both institutions.

Results

A. Resting Studies

Thirty studies were interpreted by three experienced nuclear medicine physicians without knowledge of the patient's name or history. In cases of disagreement between physicians, the majority opinion governed. Eleven studies were interpreted as abnormal. The results of the left ventricular angiogram (LVA), the resting EKG and the coronary arteriogram (CA) for these eleven patients are shown in Table II. All eleven had a positive LVA and CA. Three of the eleven had an equivocal resting EKG while the other eight had an EKG suggestive of a previous myocardial infarction. Shown in Table III are the results for fifteen of the nineteen negative ^{201}Tl studies. Four normal thallium images, not included in this table because they did not receive a CA or LVA, had a normal stress test and EKG and no history of a previous myocardial infarction. If it is assumed that the LVA is the "Gold Standard" against which we must compare the ^{201}Tl study for clinical accuracy and utility, then Tables II and III show that the ^{201}Tl image had a true positive rate of 73%, a false positive rate of 0% and a false negative rate of 27%. This is contrasted with the resting EKG which had a true positive rate of 53%. In all eight cases where the resting EKG was positive, the thallium image was positive and the correlation was 100% for predicting the site of myocardial damage. In the seven cases where the EKG was equivocal the LVA showed abnormality to be present in four of them and of these four, three had a positive ^{201}Tl study. Of the fifteen cases with proven heart wall damage by the LVA, four had a normal thallium study. One of these had hypokinesia of the inferior wall, one apical akinesia, another had an aneurysm of the anterior wall and the fourth patient had global hypokinesia of the left ventricle. In the other eleven cases of abnormal LVA the thallium image showed equal or greater damage to the ventricular wall.

B. Stress Studies

All thallium images were evaluated independently by a specialist in nuclear medicine and by a board certified cardiologist with extensive training in nuclear cardiology. An image was judged positive if there was an area of abnormally decreased myocardial thallium uptake on the stress images. The defect was considered to represent transient myocardial ischemia (transiently positive) if the defect filled in with ^{201}Tl prior to the repeat imaging performed 4-6 hours after the stress study. The defect was considered permanently positive if there was no change in relative activity when the stress and resting images were compared.

Coronary artery narrowing was considered significant and, therefore, resulting in (transient) ischemia if the luminal diameter was narrowed by more than 75%.

The routine treadmill testing was performed with multiple graded levels of exercise during continuous electrocardiographic recording. The patient was stressed to 85% of predicted maximal heart rate on the basis of age and sex. The treadmill test was considered positive if the ST segment was displaced downward by more than 1 mm in one or more leads. The absence of diagnostic ST changes in the presence of an 85% maximum heart rate response was called a negative treadmill test.

Shown in Table IV are the results in 28 patients who underwent coronary arteriography and a ^{201}Tl stress study. Two of the 28 patients had both transiently and permanently positive images. Two patients judged to have significant arteriographic lesions had negative images giving a false negative rate of 18% for detecting ischemic heart disease. The overall true positive rate of the ^{201}Tl stress study to detect patients with abnormal coronary arteriograms was 90%. There were 4 false positive ^{201}Tl images as follows:

1. One had proven coronary artery spasm at the time of the ^{201}Tl injection during cardiac catherization and atrial pacing. This hyperactive vascular response caused transient narrowing of the coronary artery which was relieved by nitroglycerine. This patient serves to emphasize that myocardial ischemia and even infarction is known to occur with "normal" coronary arteries, i.e., in the absence of demonstrable fixed coronary atherosclerotic lesions (7).

2. One had a completely normal cardiac catheterization study, a left bundle branch block and a nondiagnostic treadmill because of the presence of the abnormal conduction pattern.

3. One had impairment of left ventricular function with elevated left ventricular end-diastolic pressures, a non-obstructive lesion of the right coronary artery and was diagnosed as a presumed cardiomyopathy. The thallium image showed transient anteroseptal ischemia.

4. One had a normal cardiac catherization study although left ventriculography was not performed.

The treadmill stress tests and the coronary arteriogram results of the 23 of the 28 patients are shown in Table V. The significant finding here is the high incidence of either false negative (3) or nondiagnostic (6) treadmill results in patients with lesions. These represent 56% of the patients with positive arteriograms. Unfortunately many of the patients who receive treadmill tests are unable to exercise sufficiently to achieve a high heart rate. This may be due to several factors including the presence of vascular disease in the legs which causes claudication with exercise, physical disabilities like arthritis of the knees, marked physical deconditioning as is common in the hospitalized patients and, moreover, Inderal, one of the mainstays of treatment of angina pectoris causes a definite slowing of the heart and many of the patients taking Inderal are simply unable to achieve 85% of their maximum heart rate.

Besides heart rate limitations, there are other conditions that interfere with interpretation of the changes on the exercise electrocardiogram. These include the presence of intraventricular conduction defects which affect the ST interval at rest and the presence of left ventricular hypertrophy which also changes the ST segments at rest. Digitalis causes unpredictable changes in repolarization that may cause false positive and false negative treadmill responses. Wolff-Parkinson-White syndrome, a syndrome of abnormal preexcitation of the ventricles with abnormally shortened P-R interval, also interferes with the interpretation of the treadmill response. Therefore, we looked at the number of treadmills with inconclusive or nondiagnostic ST responses and compared them with the coronary arteriograms. Although the numbers are small, there were 7 of 23 patients whose treadmill tests were inconclusive and who would require additional tests or coronary arteriography to ascertain the presence or absence of coronary artery disease. Interestingly, of these patients only one with an inconclusive treadmill test had normal coronary arteriography--presumably this is a result of the prior selection process occurring with the referring physician.

When the results of the thallium study and the treadmill are combined and the patient with either one or the other test positive are evaluated for the presence of coronary artery disease, several interesting conclusions can be reached (Table VI). There is an increase in the false positive tests while there is a fall in the false negatives. Therefore, these two tests combined are more sensitive than either alone for detecting the presence of coronary artery disease, but the overall specificity falls. The false negative rate decreases to about 6%.

Since these studies were obtained with new improved nuclear medicine equipment, it was considered useful to attempt to compare positive resting images with left ventriculography. The image obtained 4-6 hours after the injection given during stress was assumed to be the equivalent to an image after the patient was injected at rest. The left ventriculography was performed in the 30^{0} RAO projection. Abnormalities were judged as showing hypokinesis or akinesis according to published criteria (8).

The data in Table VII can be used to compare the resting image with left ventriculography. In only two cases the ^{201}Tl images were interpreted as normal in the presence of definite myocardial damage, i.e., false negative rate of 12.5%. This is significantly better than the 27% false negative rate obtained using the older equipment (part A of results).

In other studies the presence of severe three vessel disease has been correlated with false negative thallium image. We have found one instance of this occurring. This patient had high grade involvement of the right coronary artery, the proximal left anterior descending and a large obtuse marginal vessel arising from the left circumflex artery. Evaluating our group of patients shows that there were seven other patients who had severe involvement of all three coronary arteries. In all these patients there was evidence of abnormal myocardial perfusion by thallium imaging. Thus the finding of a negative image in the presence of severe triple vessel disease is not a common problem in our experience.

Conclusions

1. The thallium stress test is more specific and more sensitive than the treadmill alone for evaluating ischemic heart disease.
2. Abnormalities of resting thallium images correlate well with abnormalities documented by left ventriculography and thus with the presence of

myocardial infarction.

3. Abnormalities of either resting or stress ^{201}Tl images are highly suggestive of significant coronary artery disease.
4. Thallium stress test can show defects in the presence of a normal coronary arteriogram and may give insight into other forms of ischemic heart disease, e.g., coronary artery spasm or myocardial infarction in the presence of normal coronary arteries.
5. Severe triple vessel disease will usually result in a positive thallium image contrary to previous reports.

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TABLE I

RADIATION ABOSRBED DOSE FROM ^{201}THALLIUM

Organ	Rads/mCi
Whole Body	0.21
Testes	0.59
Kidney	1.17
Thyroid	1.03
Upper and Lower G.I.	0.90

TABLE II

POSITIVE ^{201}THALLIUM IMAGES
(11 Cases)

	Positive	Negative	Equivocal
Left Ventricle Angiogram	11	0	0
Resting EKG	8	0	3
Coronary Arteriogram	11	0	0

TABLE III

NEGATIVE ^{201}THALLIUM IMAGES
(15 Cases)+

	Positive	Negative	Equivocal
Left Ventricle Angiogram	4	11	0
Resting EKG	0	11	4*
Coronary Arteriogram	11	4	0

+Four cases not included in this table in which the L.V. and coronary angiogram were not done, the ^{201}Tl image, EKG and exercise stress tests were normal with no history of myocardial infarction.

*Only one of these four patients had a positive left ventricle angiogram.

TABLE IV

COMPARISON OF ^{201}Tl STRESS STUDY
WITH CORONARY ARTERIOGRAM

	Coronary Arteriogram	
^{201}Tl Results	Patients Without Lesions	Patients With Lesions
Transiently Positive	4*	9
Permanently Positive	0	9+
Negative	6	2

*One patient had proven coronary artery spasm from catheterization.

+Two patients had both transient and permanent ischemias, i.e., positive ^{201}Tl image at rest and exercise.

TABLE V

COMPARISON OF TREADMILL STRESS TEST VS CORONARY ARTERIOGRAM

	Coronary Arteriogram	
Treadmill Results	Patients Without Lesions	Patients with Lesions
Positive	1	7
Negative	5	3
Non-Diagnostic	1	6

TABLE VI

COMPARISON OF THE COMBINED TREADMILL AND ^{201}Tl STRESS STUDY WITH THE CORONARY ARTERIOGRAM

	Coronary Arteriogram	
Treadmill and ^{201}Tl Scan	Patients Without Lesions	Patients With Lesions
Positive*	5	15
Negative	2	1

*The result was considered positive if either the treadmill or the ^{201}Tl image were positive.

TABLE VII

COMPARISON OF RESTING ^{201}Tl IMAGE VS LEFT VENTRICULOGRAPHY*

Resting ^{201}Tl Image	Left Ventricle Angiogram Abnormal	Left Ventricle Angiogram Normal
Positive	14	2
Negative	2	8

*These images were obtained with newer computer assisted gamma camera, Elscint CE-1-7 37 PM Tube Camera and Dycomette Computer.