Clinical Outcome of Cardiac Patients with Negative Thallium-201 SPECT and Positive Rubidium-82 PET Myocardial Perfusion Imaging

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In a previous comparison of 202 consecutive patients who underwent myocardial perfusion imaging with both ^{201}Tl SPECT and ^{82}Rb PET, 27 patients were identified as having true-positive ^{82}Rb images, but false-negative ^{201}Tl images. The purpose of this report is to determine the effect of correct image interpretation of coronary artery disease on the final management of those patients and compare it to the previous management scheme wherein a negative image was usually accepted as the end point unless clinical symptoms dictated otherwise. A follow-up study of the clinical course and outcome of these studies showed that 63% (17/27) of the patients with a true-positive ^{82}Rb PET image were recommended for revascularization procedures. It is doubtful that this majority of patients would have received either surgical or interventional management based on the false-negative ^{201}Tl SPECT procedure alone.

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In our institution, and probably others, there is a high reliance on ^{201}Tl myocardial perfusion imaging in the decision making process and management of the patient with coronary artery disease (CAD) (*1*). While false-positive interpretation results would involve the patient with additional procedures and expense of coronary angiography, false-negative interpretation results could have the more serious consequence of the patient receiving neither subsequent coronary angiography, if needed, nor the proper indicated medical care.

A population in which false-negative myocardial perfusion ^{201}Tl SPECT studies could be analyzed was available from a previous comparison of 202 consecutive patients evaluated for coronary artery disease with both ^{201}Tl SPECT and ^{82}Rb PET myocardial perfusion imaging (*2*). From these 202 patients, 27 were identified as true-positive by the ^{82}Rb PET study but as false-negative by the ^{201}Tl images. The majority of these discrepancies involved the inferior-posterior left ventricular segments which in some cases showed only a moderate degree of coronary stenosis (*3*).

The purpose of this study was to determine the effect of image interpretation on the final management of these patients with CAD and compare it to what would be expected by the previous routine management scheme in which a negative image was usually accepted as the end point. For this reason, a follow-up study of the clinical course and outcome of these patients was performed.

PATIENTS AND METHODS

Patients

The characteristics of the 27 patients are shown in Table 1. Nine patients had single-vessel disease, ten had two-vessel disease and eight had three-vessel disease (Fig. 1A). Fifteen of the ^{82}Rb images had persistent defects (scar) and twelve patients exhibited transient defects (ischemia) only.

Forty-one percent (11/27) of the present study had previous revascularization procedures and 30% (8/27) had previous myocardial infarction (MI) (Fig. 1B). As shown in Table 1 and Figure 2, the most common perfusion defects involved the inferior or posterior wall, with 81% (22/27) of the subjects having a perfusion defect in that area, 7% (2/27) having defects in the distal septum alone, 7% (2/27) in the anterior, antero-septal or apical segment and 4% (1/27) in the mid-lateral segment only.

Data Acquisition

PET imaging was performed with the Posicam System (Positron Corp., Houston, TX) using a 256 × 256 matrix and obtaining 21 slices, each approximately 5.1 mm thick. The attenuation correction was applied based on a ^{68}Ga plexiglass ring transmission image. Reconstruction was made with the Positron Data Acquisition System (PDAS, Positron Corp., Houston, TX) utilizing backprojection with a Butterworth filter of order five and cutoff of 0.4.

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TABLE 1
Outcome of Patient Management Following Myocardial Perfusion Imaging Positive with ^{82}Rb but Negative with ^{201}Tl

Patient characteristics of prior to ^{82}Rb PET						Defect site Detection by ^{82}Rb PET					Revascularization	
			Angiographic results (% stenosis)									
Patient No.	Previous MI	Previous Intervention	LAD	CX	RCA	Date of ^{82}Rb PET	Anterior apex	Septum	Inferior posterior wall	Lateral wall	Date	Type
5	No	O	—	—	95%	9/20/88	—	—	(f)+	—	9/6/90	B
7	No	B	80% G	80%	100%	9/22/88		(t)+	(t)+	—	1/11/89	B
25	No	P	60%	—	—	10/11/88	—	—	(t)+	(t)+	11/9/88	P
49	No	P,B	100% G	100%	100% G	11/8/88	—	—	(f)+	—	9/1/89	B
52	No	O	60%	—	50%	11/22/88	—	(t)+	—	—	5/18/89	B
			80% D									
60	No	B	100% G	90%	80%	11/30/88	—	—	(f)+	—	no revas.	O
67	Yes	P,B	—	—	100% G	12/8/88	—	(t)+	(t)+	—	no revas.	O
73	No	O	—	90%	80%	12/9/88	—	—	(f)+	(f)+	2/16/89	B
74	Yes	O	—	50%	100%	12/12/88	—	—	(t)+	—	no revas.	O
77	Yes	O	75%	90%	70%	12/13/88	—	—	(f)+	(t)+	no revas.	O
108	No	O	—	—	90%	4/6/89	—	—	(t)+	—	4/10/89	P
110	No	P	—	60%	—	4/11/89	—	—	(t)+	(t)+	11/30/89	P
116	Yes	O	80%	70%	100%	4/18/89	—	—	(t)+	—	no revas.	O
120	No	O	80%		50%	6/6/89	(t)+	(t)+	(f)+	—	6/8/89	P
					D 70%						8/3/89	P
128	No	B	50% G	75%	100%	6/15/89	—	—	(f)+	—	11/30/89	P
131	Yes	O	90% D	—	—	6/21/89	(f)+	(f)+	—	—	10/1/90	P
											4/30/91	B
135	No	O	35%	—	80%	6/26/89	(f)+	—	(f)+	—	2/5/91	B
137	Yes	O	70% D	—	60%	6/27/89	—	—	(t)+	—	no revas.	O
									(f)+			
143	Yes	P	100% G	—	100%	7/5/89	—	—	(f)+	—	2/27/90	P
153	No	O	80%	—	—	7/19/89	(t)+	—	—	—	no revas.	O
161	No	B	—	100%	100%	7/27/89	—	—	—	(f)+	10/23/89	B
164	No	O	—	—	60%	8/1/89	—	(t)+	(t)+	—	no revas.	O
168	No	O	55%	—	—	8/3/89	(f)+	—	(f)+	—	no revas.	O
177	No	O	50%	90%	90%	8/10/89	—	(t)+	—	—	2/11/92	B
186	Yes	B	85% G	100% G	100% G	8/24/89	—	—	(f)+	—	8/28/89	B
201	No	B	55% G	—	70% G	9/13/89	(f)+	—	(t)+	—	9/14/89	P
209	No	O	60%	—	70%	10/4/89	—	—	(t)+	—	no revas.	O

P = PTCA, B = CABG, O = none, f = fixed defect, t = transient defect, G = patent graft and D = diagonal.

SPECT imaging was performed with a three-headed TRIAD scintillation camera (Trionix Inc., Twinsburg, OH) and recorded on a 64 × 64 matrix for 32 slices with a thickness of 7.1 mm each. Reconstruction was performed by a Sun computer on the TRIAD by backprojection using a Hamming filter with a cutoff of 0.7. Details of these measurements have been previously described (*2*).

Imaging Protocol

Following the transmission image, ^{82}Rb was injected into the patient through an intravenous infusion line. After a delay of 65 sec, data were collected for the resting image over a period of 7 min. Following the rest study, dipyridamole was infused intravenously for 4 min to induce coronary vasodilatation. The patient started isometric hand-grip exercise at 25% maximum strength at 2 min after the completion of dipyridamole infusion (*4*). At 4 min after the end of the dipyridamole infusion, ^{82}Rb was again infused while maintaining the hand-grip for an additional 2 min. Stress ^{82}Rb image data were collected for 4 min starting 65

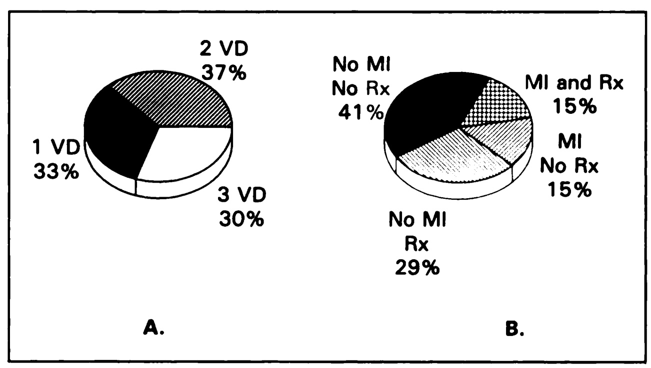

FIGURE 1. Extent of coronary disease in the 27 patients with false-negative ^{201}Tl SPECT and true-positive ^{82}Rb PET images. (A) Distribution of patients with single-, double- and triple-vessel disease. (B) Previous history as to myocardial infarction and revascularization. Note that 44% had revascularization procedures previous to the present evaluation.

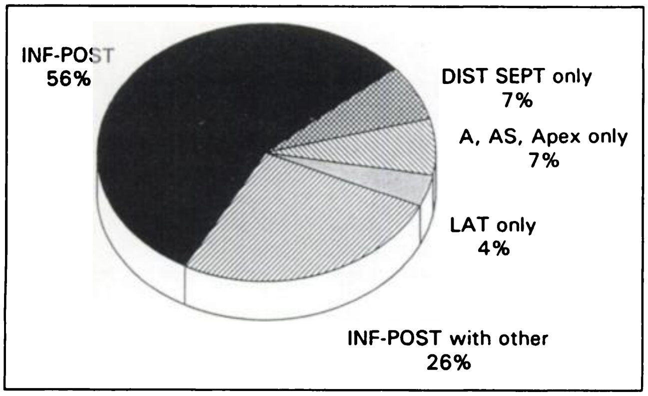

FIGURE 2. Site of lesions missed with ^{201}Tl SPECT false-negative images. Eighty-two percent involved the inferior-posterior wall.

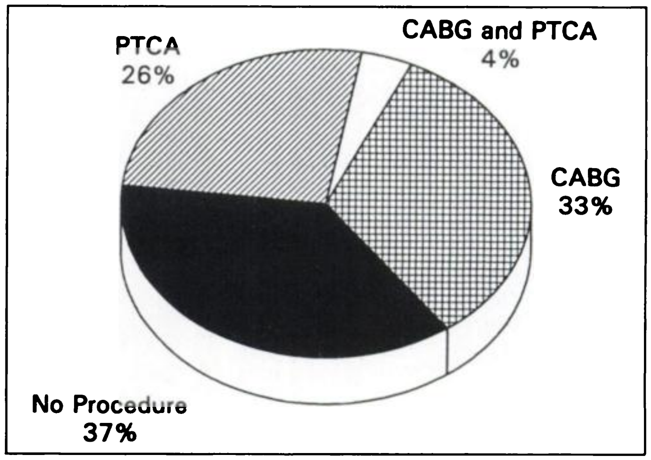

FIGURE 3. Revascularization procedures received by 17 of the 27 patients with false-negative ^{201}Tl SPECT images.

sec after tracer administration. Immediately following ^{82}Rb stress data acquisition, ^{201}Tl was injected intravenously through the infusion line and stress ^{201}Tl SPECT data acquisition was initiated using the TRIAD camera. Redistribution ^{201}Tl SPECT images were recorded 3–4 hr later.

Image Interpretation

Images were displayed with segmental color scales of 10% and 5% differences for quantitative interpretation (*2*). Previous studies (*5,6*) have determined that myocardial segments would be considered normal if the count variation between segments were within 20% or less when compared to the segment with the highest count rate for ^{201}Tl or ^{82}Rb. A higher range of decreased count rates of 30%–40% was allowed for the apex and diaphragmatic segments for ^{201}Tl because of known variations in attenuation and scatter. These same segments were allowed only 20%–30% for the ^{82}Rb studies. For segments to be designated as ischemic, a decrease in count rate of more than the above normal limits must occur at stress and the segments increasing in count at rest or redistribution by 20% or greater. Where there was less than 20% fill-in, scar was designated. Details of this methodology have been previously described (*2*).

RESULTS

In a review of the patients' records up to May 1992, 17 of the 27 patients (63%) received revascularization procedures as shown in Figure 3. Nine received CABG, seven PTCA (one had PTCA twice), and one patient had both PTCA and CABG. Five patients had revascularization procedures within a week following image interpretation, an additional eight had revascularization in 1–10 mo and the remaining four patients from 1–2.5 yr following the original PET imaging interpretation.

Of the ten subjects who did not receive revascularization procedures, five had single-vessel disease with stenoses ranging from 55% to 100%, two had double-vessel disease of 60% and 70%, and three had triple-vessel disease with previous MI or revascularization prior to the radionuclide imaging procedures.

The complete revascularization data are shown in Table 1. While the overall rate of subsequent revascularization was 63%, those subjects with previous therapeutic interventions received the highest rate of revascularization (9/11 or 82%). Those patients without previous therapeutic intervention had a lower rate of subsequent revascularization (8/16 or 50%), as did patients with transient ^{82}Rb defects only (6/12). The lowest rate of revascularization (3/8 or 38%) was exhibited by those with previous myocardial infarction.

DISCUSSION

Previous studies from our institution during the pre-PET era have shown that in a randomly selected sample of 276 patients in 3 mo, there were 179 cases with negative ^{201}Tl SPECT studies. Ninety-six were de novo patients with no previous coronary angiography and 83 were patients referred for evaluation of recent revascularization or were patients with known critical or subcritical lesions. All 83 patients had remote coronary angiography prior to the ^{201}Tl SPECT study. Review of the subsequent management of these patients showed that only 4 of the 179 patients (2%) had coronary angiography following the negative ^{201}Tl SPECT procedure (*7*). This study indicates that a negative myocardial perfusion image correlates strongly with the decision of the cardiologists to avoid aggressive invasive diagnostic follow-ups unless clinical symptoms dictated otherwise.

It is realized, however, that the population from which the 27 discrepancies were drawn (*2*) differs considerably from the above routine population. It is difficult to ascertain the exact role of the results of the positive PET scan in the decision making for management of these 27 patients. Management was complicated by the large variation in the time of revascularization following the PET procedure and the uncertainty of whether any revascularization had been planned before the studies. The fact that the negative ^{201}Tl image inhibits further aggressive procedures suggests that it would be doubtful that the 17

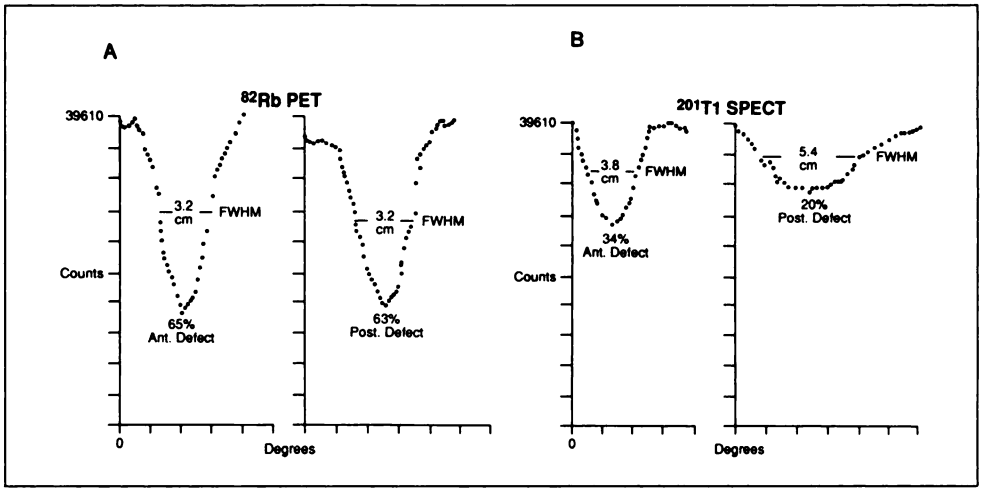

FIGURE 4. Profiles taken from a cardiac phantom with 2-cm lesions placed on both the anterior and posterior walls. (A) Little difference is seen with placement when recorded with ^{82}Rb PET, but the degradation in the posterior lesion with ^{201}Tl SPECT would place an obvious lesion seen with PET in the equivocal range with SPECT (B).

patients in the present series with false-negative ^{201}Tl SPECT images would have had the revascularization procedures performed were it not for the results in the true-positive ^{82}Rb PET images. The PET scan must then be considered necessary to provide appropriate medical care for these patients, but it cannot be determined what actual weight the PET scan had on the final decision.

It should be noted that in the original report of 202 patients, the reverse situation of a false-negative ^{82}Rb PET study in the presence of a true-positive ^{201}Tl SPECT never occurred (*2*).

Although the sensitivity of ^{201}Tl SPECT myocardial perfusion imaging has been satisfactory, it has often been achieved at the expense of lower specificity (*8,9,10*). When the values of sensitivity and specificity are more balanced, the adjustment of the normal/abnormal criteria would predict an increase of specificity, but with a decrease in sensitivity (*11*). The incidence of increased false negative ^{201}Tl SPECT images (27/152, or 18%) relative to ^{82}Rb PET is not unexpected, but that 11% (17/152) would have had inadequate follow-up, including revascularization without ^{82}Rb PET, indicates a serious deficiency in conventional health care if one were to rely on ^{201}Tl SPECT imaging as the end point in diagnosing CAD.

The low sensitivity of myocardial ^{201}Tl SPECT compared to the higher sensitivity of the ^{82}Rb PET procedure, particularly in the inferior and posterior walls, has been attributed to less accurate attenuation correction and large scatter fraction in SPECT (*2*). To illustrate this difference, Figure 4 shows count rate profiles obtained from a cardiac phantom with simulated 2-cm anterior and posterior lesions (Model 7070 Data Spectrum Corporation, Chapel Hill, NC) placed in an elliptical water-filled thorax phantom comparing ^{201}Tl or ^{82}Rb. While the FWHMs of the anterior lesions compare reasonably well between ^{201}Tl and ^{82}Rb (3.8 and 3.2 cm), the FWHM of the posterior lesion on ^{201}Tl (5.4 cm) is considerably degraded compared to that of ^{82}Rb (3.8 cm).

This measurement demonstrates the dramatic decrease in contrast resolution with ^{201}Tl SPECT for lesions on the posterior or inferior wall. Acceptance of a minimum of a 20% drop in count rate as a criterion for a defect in the posterior or inferior wall, compared to normal tissue, would increase the sensitivity of the test but result in lower specificity by producing many more false-positives. Although improved SPECT attenuation programs can be expected in the future, the scatter, unfortunately, is strongly dependent on gamma ray energy and little actual improvement can be foreseen for ^{201}Tl myocardial perfusion imaging.

CONCLUSION

Since myocardial imaging is strongly influential in subsequent management of the CAD patient, it is important that the test chosen has a high sensitivity so that patients with CAD requiring either invasive therapeutic procedures or medical treatment can be identified. This high sensitivity should be paralleled with high specificity so that needless invasive coronary angiographic procedures can be minimized.

In this report, it is emphasized that 18% (27/152) of an abnormal population had false-negative ^{201}Tl SPECT but true-positive ^{82}Rb PET interpretation. That 63% (17/27) of these patients received a revascularization procedure demonstrates the importance of the true-positive ^{82}Rb PET study and makes this technique the procedure of choice, particularly in those patients with a perfusion defect involving the diaphragmatic segment of the left ventricular myocardium.

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SELF-STUDY TEST
Gastrointestinal Nuclear Medicine

ANSWERS *(continued)*

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Items 7-10: Barrett's Esophagus

Answers: 7, F; 8, F; 9, F; 10, F

Much has been written about the clinical presentation and assessment of patients with Barrett's esophagus. Although Barrett's esophagus causes no symptoms per se, the clinical presentation is related to gastroesophageal reflux and covers the spectrum of regurgitation, heartburn, chest and abdominal pain, and dysphagia. It has been suggested that patients with Barrett's esophagus have less severe symptoms than do those with reflux esophagitis without Barrett's epithelium. The five major complications of Barrett's esophagus include: esophagitis, ulceration, stricture, bleeding, and adenocarcinoma (not squamous cell cancer). The frequency of adenocarcinoma of the esophagus in patients with Barrett's esophagus is approximately 10%. The risk of esophageal cancer with Barrett's esophagus is approximately 30 to 40 times greater than that in the general population. Once the diagnosis of Barrett's esophagus has been made on biopsy, periodic endoscopy with biopsy is recommended to monitor for malignant transformation. The radiographic appearance of Barrett's esophagus is not specific and includes gastroesophageal reflux, hiatal hernia, esophageal stricture, ulceration, irregular mucosal folds, granulating reticular mucosal pattern, and intramural pseudodiverticulosis. The findings of a benign-appearing stricture in the proximal esophagus or a deep esophageal ulceration should suggest the diagnosis and prompt endoscopic evaluation. The scintigraphic assessment of Barrett's esophagus has not been widely explored or utilized. The accumulation of ^{99m}Tc pertechnetate in the lower esophagus after intravenous injection of this tracer is considered a positive examination and is related to mucous-secreting cells of Barrett's mucosa. The swallowing of free ^{99m}Tc in saliva and eflux of gastric activity can cause significant problems in scan interpretation, however. Scintigraphy can identify possible areas of Barrett's esophagus, but plays no role in assessment for possible malignancy. Currently, scintigraphy plays no definitive role in the evaluation of patients with suspected Barrett's esophagus. A large prospective study with adequate controls will be necessary to define if any future role for scintigraphy exists.

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Items 11-15: Peritoneovenous Shunt Imaging

Answers:11, F; 12, F; 13, T; 14, T; 15, T

Scintigraphic techniques for assessing patency of peritoneovenous shunts utilize tracers injected into the peritoneal cavity and/or directly into the efferent limb of the shunt. These imaging techniques monitor the transit of tracer from the peritoneal cavity through the shunt into the target organs (lung or liver/spleen) of the tracer employed (^{99m}Tc macroaggregated albumin +MAA or ^{99m}Tc sulfur colloid). The most frequent cause of shunt malfunction is obstruction by fibrin deposits of the afferent limb of the shunt. Less frequently, thrombus formation occurs in the efferent portion of the tubing. When ^{99m}Tc MAA is the tracer utilized at high and low flow rates, there may be nonvisualization of the efferent shunt tubing. Hence, direct target organ visualization i.e., tracer accumulation in the lungs should be utilized as the criterion of shunt patency. Disease states that cause elevated right heart pressure, such as congestive heart failure, can cause false-positive studies. Thus, when only the afferent portion of the shunt is visualized, direct puncture of the efferent limb is generally necessary to locate the site of malfunction more precisely. Both the sensitivity and specificity of peritoneovenous shunt scintigraphy appear to be high. In a study of 40 patients, six of whom were evaluated when their shunts appeared to be malfunctioning, no false-positive or false-negative studies were encountered.

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