Uptake of Myocardial Imaging Agents by Rejecting and Nonrejecting Cardiac Transplants. A Comparative Clinical Study of Thallium-201, Technetium-99m, and Gallium-67

Shuhei Yamamoto, Jacob Bergsland, Susan M. Michalek, Mary Carroll, Jayakumari M. Gona, Daya Balu, and Edward A. Carr, Jr.

Buffalo Veterans Administration Medical Center and Departments of Surgery, Pharmacology and Therapeutics, Medicine, Pathology and Medical Technology, The State University of New York at Buffalo, Buffalo, New York

To study the scintigraphic detectability of cardiac rejection, we performed 135 planar myocardial scans ([^{99m}Tc] pyrophosphate, 85; ^{201}T1, 36; ^{67}Ga, 14) together with endomyocardial biopsies in ten patients for a (mean) 17-mo postoperative period. Specificity of each agent exceeded 89%. Technetium-99m pyrophosphate showed results that significantly correlated with the severity of rejection ($p = 0.03$), as shown by biopsy, but neither ^{201}T1 nor ^{67}Ga did so ($p = 0.63$ and 0.81, respectively). Technetium-99m pyrophosphate showed better diagnostic accuracy (85%) than ^{201}T1 (69%) and ^{67}Ga (64%). Technetium-99m pyrophosphate also showed higher negative predictive value (91%) than thallium (76%) and gallium (69%). Thus, a normal ^{99m}Tc pyrophosphate scan was usually associated with absence of cardiac rejection. However, all three agents showed unacceptably poor sensitivity (0% to 30%) and thus were not useful as a screening test for cardiac rejection, even when the same agent was used serially in imaging a given patient.

J Nucl Med 30:1464–1469, 1989

Right ventricular endomyocardial biopsies have been employed clinically for detection of cardiac rejection (*1*). But more recently, a growing number of experimental (*2–10*) and clinical (*11–20*) studies of the uptake of various radiopharmaceuticals in cardiac rejection have been reported. In our rat heterotopic transplantation model (*7*) cardiac rejection was characterized by decreased uptake of thallium-201 (^{201}T1) and increased uptake of both technetium-99m (^{99m}Tc) pyrophosphate and gallium-67 (^{67}Ga), reflecting the underlying pathophysiologies (i.e., myocardial hypoperfusion, myocytolysis, and intramyocardial leukocyte infiltration, respectively). In clinical cardiac transplantation several studies have been directed at the possibility that decreased myocardial uptake of thallium-201 (*11–14*) or increased uptake of gallium-67 (*15–16*) or technetium-99m (*17*) might permit scintigraphic detection of acute rejection. Despite the encouraging results of the several studies in animals, the results of the clinical investigations of individual imaging agents have been less satisfactory. Even different studies of the same imaging agent have led to differing estimates of the value of that agent for detection of clinical rejection (*15–16*). To our knowledge there is as yet no clinical report of a comparative study of all three agents for this purpose. Moreover, the potential usefulness of these agents for follow-up by serial imaging over a period of time is not known. In order to investigate these questions, we performed repeated cardiac imaging studies in a group of patients, using these three agents singly or in combination, together with endomyocardial biopsy.

Received July 5, 1988; revision accepted May 16, 1989.

For reprints contact: Edward A. Carr, Jr., MD, Dept. of Pharmacology and Therapeutics, State University of New York at Buffalo, 102 Farber Hall, Buffalo, NY 14214.

SUBJECTS

Our study group consisted of ten patients, nine men and one woman, aged 24 to 56 yr at operation (Table 1), who underwent orthotopic cardiac transplantation from 1984 through 1987 in our institution. The etiologies were atherosclerotic heart disease (Patients 2, 3, 4, 6, and 8), alcoholic cardiomyopathy (Patients 5, 10), or both (Patient 7), familial cardiomyopathy (Patient 1) and rheumatic heart disease (Patient 9). All operations were performed uneventfully and were without major perioperative morbidity. In each patient the follow-up period covered the time, ranging from 2 to 35 mo, from operation to December, 1987. Informed written consent was obtained from each patient before the study.

METHODS

Transvenous right ventricular endomyocardial biopsy: this was performed in the standard manner and frequency (*1*) (two to four times within the first postoperative month, monthly thereafter up to 6 mo, then yearly). The biopsy specimens were interpreted (*21*) as either normal or showing rejection, which was expressed as *resolved* (fibrosis only), *resolving* (fibrosis with diminishing residual mononuclear cells), *mild* (fibrosis, interstitial edema, or both, plus infiltration by mononuclear cells), *moderate* (myocytolysis, more marked fibrosis, edema, or their combination, plus manifest infiltration by mononuclear cells), or *severe* (addition of neutrophils, microthrombi, and interstitial hemorrhage).

Immunosuppressive therapy. Oral maintenance therapy consisted of cyclosporine A (1.5–3.0 mg/kg body weight) plus either prednisolone (10–20 mg/day) or azathioprine (75–150 mg/day). Unresponsive patients were treated with all three drugs. Episodes of acute rejection were treated by augmented immunosuppression (i.v. methylprednisolone, antithymocyte globulin, or both), until resolving or resolved rejection was documented by weekly biopsy. Mild rejection with very slight infiltration by mononuclear cells, however, was not so treated and maintenance therapy was continued.

Planar myocardial imaging. Two gamma cameras, ZLC LFOV (Siemens) and GE 400T Maxicamera, were used. Both had a high-resolution collimator and were interfaced to an A^2 MDS Computer. In each patient imaging was done using either [^{201}Tl]chloride (*74 MBq*), [^{99m}Tc] pyrophosphate (*370–555 MBq*) or [^{67}Ga]citrate (*111-259 MBq*) as follows. Imaging was started at 20 min, 2 hr, and 24 hr postinjection, respectively, with preset counts of 400,000, 600,000 and 300,000, respectively. Gallium imaging was repeated at 48 hr and, when possible, 72 hr postinjection. In gallium imaging, a preset time of 10 min was also used. Energy window was set at 80 keV (± 20%) for thallium, at 140 keV (±20%) for technetium, and at double peak of 184 keV (±20%) and 300 keV (±15%) for gallium. The acquisition matrix was 128 × 128 in all images. In thallium and technetium studies, images were obtained from an anterior view and from 30- to 70-degree left anterior oblique views. In gallium studies a spot image was obtained from an anterior view. Thallium images were routinely subjected to background subtraction processing.

For optimum utilization of this small series of patients, the difference in radiation exposure (gallium > thallium > technetium) was considered. Selection of imaging agents was made as follows (*1–4*).

Technetium was the chief agent used in six patients; two patients received only thallium. Technetium was combined (both agents given within 2 days of a single biopsy) with thallium during part of the study of Patients 1, 5, and 6, and

TABLE 1
Endomyocardial Biopsies Performed (Including Dates of Documented Cardiac Rejection) and Cardiac Scintigrams Analyzed in Ten Patients After Cardiac Transplantation

Patient no.	Age*/sex	Follow-up period (mo)	Endomyocardial biopsy			Scintigraphic studies		
			No. performed	No. showing rejection	Time of rejection†	Tc (n)	Tl (n)	Ga (n)
1	24/F	30	20	5	(2w,3w,1m,16m,17m)	9	3	1
2	40/M	4	8	1	(2w)	3	0	4
3	41/M	18	19	2	(7m,18m)	14	0	3
4	44/M	4	8	1	(2w)	0	6	0
5	45/M	31	20	0		20	10	0
6	48/M	12	20	6	(1w,1m,2m,3m,5m,10m)	6	9	0
7	53/M	12	22	5	(4w,2m,3m,4m,7m)	12	1	3
8	53/M	18	20	3	(1w,1m,3m)	13	1	3
9	54/M	35	17	5	(1w,2w,3w,7m,16m)	8	2	0
10	56/M	2‡	6	1	(2w)	0	4	0
Sum		166	160	(29)		85	36	14

Ga = [^{67}Ga]citrate; Tc = [^{99m}Tc]pyrophosphate; Tl = [^{201}Tl]chloride.
* At operation.
† The suffixes (d, w, m) denote day, week, and month after operation, respectively.
‡ Died of a gastrointestinal hemorrhage, with onset while patient was at home.

with gallium during part of the study of Patients 2, 3, 7, and 8, respectively.

In all these schedules, if an imaging agent gave two false-negative results in any given patient, that patient's assignment was changed to another agent; an exception was Patient 6, in whom thallium studies were still continued as part of a separate investigation.

To compare the differences in diagnostic reliability among the three agents, all scintigrams were read simply as abnormal (i.e., "positive", indicating rejection) or normal ("negative"). The aforementioned animal studies (*3–5, 7*), all with histologic confirmation, support the view that the abnormality to be expected in acute rejection is increased gallium as well as technetium uptake but decreased thallium uptake. Previous clinical studies have also been based on acceptance of this view (*8, 11–17*). Thus, for thallium, either localized or diffuse loss of uptake in any left ventricular segments was defined as positive. For gallium and technetium, myocardial accumulation of any degree was defined as positive. Gallium required imaging on consecutive days; thus, a gallium study was considered abnormal if any of the series of images was abnormal. Reading was first done by two independent blinded observers. If readings were discordant, a third blinded observer served as arbiter. All readers were blinded to the result of the endomyocardial biopsy performed at that time until after the scintigraphic readings were recorded. The pathologist reading the biopsy was similarly blinded to the scintigraphic results. Scintigram readers were allowed access to scintigrams taken at the time of each patient's *previous* biopsies and to the results of those biopsies.

We report here the results of 135 studies (technetium, 85; thallium, 36; gallium, 14), which were selected using the following three exclusion criteria.

1. Imaging performed more than 2 days before or after biopsy was excluded.

2. Whenever, as a result of biopsy reports of significant rejection or a change in the patient's clinical condition, a large intravenous dose of methylprednisolone was given, or any other abrupt increase in immunosuppressive therapy occurred, all subsequent scintigrams in that patient were excluded from analysis until after a subsequent biopsy had shown resolving or resolved rejection. On occasion we have seen rapid changes in biopsies taken at short intervals, e.g., within two days, after abrupt changes in therapy. Unless serial scintigrams were taken at very short intervals to coincide exactly with the times of biopsy during such transition periods, it might be misleading to attempt correlations between scintigrams and biopsies.

3. Imaging accompanied by an unsuccessful biopsy procedure, i.e., when insufficient tissue was obtained, was also excluded.

Statistics. For each of the three (thallium, technetium, and gallium) agents, correlation between pathology and scintigraphy was analyzed by chi-square test. Endomyocardial biopsy results were scored as 1 (for normal result and resolved or resolving rejection), and 2 through 4 (for mild, moderate and severe rejection, respectively). The diagnostic reliability of each imaging agent (accuracy, sensitivity, specificity, and positive and negative predictive values) for detection of cardiac rejection was also calculated by classifying the imaging results as true or false according to the biopsy results. As we were particularly interested in determining the sensitivity of each agent as a possible screening test for rejection, even mild rejection in the biopsy, i.e., cellular infiltration of any degree as well as isolated perivascular cuffing of cells, was defined as positive. Comparison of diagnostic reliability among the three agents was by the chi-square test. A p value less than 0.05 was considered significant and a value $\geq 0.05 < 0.10$ was considered of borderline significance.

RESULTS

Table 1 gives the number of biopsies performed in each patient, plus data on rejection. In a total follow-up period of 166 patient-months acute rejection of mild or moderate degree was found in 29 of the 160 biopsies performed and in nine of the ten patients studied. Severe rejection was not found in any patient. In our patient group, rejection clustered in the postoperative period from the second to fourth week (eight of the ten patients). In all the patients except Patient 5, who had no rejection throughout his follow-up period, transplant rejection was successfully reversed within 2 wk by augmented therapy with i.v. methylprednisolone, used as either pulse therapy (500–1,000 mg, 1 to 2 times/day for 1 to 2 days) or decrement therapy (100 mg/day as starting dose, decreased over 5–10 days). Antithymocyte globulin (ATGAM), in a dose of 15 g/kg body weight for 7 days, was used one time in Patients 1 and 10.

Table 1 also lists the number of thallium, technetium, and gallium studies selected for analysis in each patient, totaling 135 studies. (Because of the exclusion criteria employed, only 22 of the 29 positive biopsies fell into the group of biopsies used to judge the accuracy of the 135 scintigraphic studies reported here; the other seven positive biopsies were associated with studies excluded from analysis by the criteria listed above.) The diagnostic reliability of each agent for detecting of rejection is shown in Table 2. For each imaging agent, true-negative results predominated. The negative predictive value of technetium was better ($p = 0.04$) than that of gallium or thallium. But the completely unsatisfactory sensitivity of all three agents was the predominant finding. Only three true positives were obtained, all with technetium. They showed diffuse accumulation over the left ventricular wall area in a doughnut pattern. Specificities were ≥89% for all three agents. The overall diagnostic accuracy of technetium (85%) appeared superior to that of thallium (69%) or gallium (64%) ($p = 0.07$). Whereas the failure to achieve sensitivity rendered technetium as unsatisfactory as the other agents for practical purposes, the histopathologic grade of the biopsies, based on the criteria listed above, correlated significantly with the outcome of technetium imaging ($p = 0.03$, Table 3) but not with gallium or thallium imaging ($p = 0.81$ and 0.63, respectively). The histo-

TABLE 2
Diagnostic Reliability of Each of the Three Imaging Agents for Detection of Cardiac Rejection

		Tc	Ga	Tl
Number of tests		85	14	36
Cases of correct test:	true positive (n)	3	0	0
	true negative (n)	69	9	25
Cases of test error:	false positive (n)	6	1	3
	false negative (n)	7	4	8
Positive predictive value (%)		33	0	0
Negative predictive value (%)		91*	69	76
Sensitivity (%)		30	0	0
Specificity (%)		92	90	89
Diagnostic accuracy (%)		85†	64	69

Abbreviations as in Table 1.
* $p = 0.04$ (Tc vs. others).
† $p = 0.07$ (Tc vs. others).

pathologic grade of the biopsies, based on the criteria listed above, correlated significantly with the outcome of technetium imaging ($p = 0.03$, Table 2) but not with gallium or thallium imaging ($p = 0.81$ and 0.63, respectively).

False negatives occurs with each agent (Table 2). Gallium imaging of Patient 1, a nonlactating female, may have given a false negative because the agent accumulated intensely in both breasts, masking its possible accumulation in the heart. Her biopsy showed moderate rejection.

False positives also occurred with each agent (Table 2). Of the 85 technetium tests, six were false positives, each showing a diffuse accumulation in a doughnut pattern over the left ventricular wall area. Of the 14 gallium tests, one was false positive, showing a pattern of diffuse uptake over the left ventricular area. Of the 36 thallium tests, three were false positives; one of the three, on review, was considered the result of scintigraphic observer error. The other two were both obtained from Patient 6 at times 2 mo apart while his condition was stable; both showed a perfusion defect extending over the anterior and interior walls. The biopsy finding (cellular infiltration and fibrosis) on each occasion was ascribed by the pathologist to cyclosporine effect ("Quilty" effect) (*22*). This patient's coronary arteriogram was normal but his ^{99m}Tc multigated cardiac scintigrams subsequently showed diffuse hypokinesis of the left ventricular wall with the ejection fractions being 12%, 27%, 15%, 16%, and 30%, respectively, over a 4-mo period.

Our reason for excluding from analysis those scintigrams taken after abrupt changes in therapy, until a subsequent biopsy had shown resolution of rejection, were given above and the data on diagnostic reliability shown in Table 2 are based on the 135 tests remaining after all exclusions described under Methods. However, if we expand our series by including the 16 studies (seven technetium, six gallium, and three thallium) previously excluded because of abrupt change in ther-

TABLE 3
Correlation Between the Histologic Grade* of Right Ventricular Endomyocardial Biopsies and Imaging Results for Each of the Three Imaging Agents

	Technetium			Gallium			Thallium		
Biopsy grade*	(−)	(+)‡	sum	(−)	(+)	sum	(−)	(+)	sum
1 (Normal)†	69	6	75	9	1	10	25	3	28
2 (Mild)	5	3	8	2	0	2	3	0	3
3 (Moderate)	2	0	2	2	0	2	5	0	5
Sum	76	9	85	13	1	14	33	3	36
Chi-square value		6.89			0.43			0.94	
p Value		0.03			0.81			0.63	

* See text. No instance of severe rejection occurred.
† Includes resolved or resolving rejection.
‡ (−) = normal; (+) = abnormal.

apy, the values for diagnostic reliability (technetium, gallium, and thallium, respectively) change to the following: sensitivity: 23%, 0%, 0%; specificity: 92%, 93%, 87%; positive predictive value: 33%, 0%, 0%; negative predictive value: 88%, 74%, 77%; overall accuracy: 83%, 70%, 69%. In the three categories (specificity, negative predictive value and overall accuracy) in which any of the agents showed any merit, the addition of these 16 previously excluded cases caused a mean absolute change of only 2.4% (range 0–6%).

DISCUSSION

In order to be useful, a noninvasive method for detecting cardiac rejection must permit the diagnosis before rejection reaches an advanced stage. The episodes of rejection studied in the present series—all mild or moderate in degree—provided a suitable test of the value of the three agents. Moreover, the rejection rate in this series is consistent with that reported in other series and suggests that these patients were a representative sample. As the greatest current need is for a test of high sensitivity, which would permit noninvasive screening and spare most patients the need for endomyocardial biopsy, it is clear that none of the agents studied here is suitable for clinical use in detecting cardiac rejection.

There are several possible reasons for the false-negative scintigrams.

1. In our prior study, using the rat heterotopic allograft model (*7*), a significant difference in uptake between rejecting and nonrejecting hearts was observed, but the magnitude of these changes was not great, i.e., approximately twofold. Such differences, though easily detectable by in vitro tissue counting in the animal, do not appear great enough for clinical detection by imaging, even when each patient is studied serially and serves as his own control. This explanation assumes that the magnitude of uptake change in rejection is the same for both species.

2. As cardiac rejection usually occurs diffusely, distribution of an imaging agent throughout the rejecting left ventricle is likely to be homogeneous, adding to the difficulty of scintigraphic diagnosis.

3. A completely different but conceivable explanation is that some as yet unknown species-specific mechanism(s) exist(s) for the uptake of these imaging agents in cardiac rejection. As this last explanation appears very unlikely, we suggest that candidate radiopharmaceuticals showing significant myocardial uptake changes in experimental rejection in animals, and satisfactory target/non-target ratios, should still be considered reasonable candidates for study in man *provided* the change in rejection is of a high order of magnitude, at least several-fold.

Although its poor sensitivity makes technetium as unsatisfactory as the other agents from the practical standpoint, the difference between technetium and the other two agents shown in this study is of interest. As acute rejection is considered to begin with cellular infiltration and this infiltration, together with vascular damage, subsequently leads to myocytolysis, one might expect a priori that technetium, a myocytolysis marker, would prove inferior to gallium and thallium in the detection of mild to moderate rejection. But in the present study technetium was clearly superior to the other two agents in showing a correlation between scintigraphic findings and the presence or absence of rejection on biopsy. The fact that more studies were conducted with technetium than with the other two agents may have introduced some bias in favor of technetium, as the chi-square test, while appropriate here, is known to show some sample-size effect, but it is unlikely that this effect fully accounts for the differences shown. In any event, it is clear that the theoretical inferiority of a myocytolysis marker to perfusion or cellular infiltration markers for demonstrating a correlation between biopsy and scintigraphy in early or moderate rejection was not substantiated. Although one must be cautious in drawing conclusions from this single series, the findings support the possibility that significant damage to myocytes may begin in acute cardiac rejection even before the myocytes show detectable histologic changes. The results obtained with a labeled antimyosin monoclonal antibody in the detection of cardiac rejection (*19, 20*) are consistent with this view. Although slow clearance of the antibody from the blood is a practical drawback in its use, it is noteworthy that increased myocardial uptake of the labeled antibody, which binds to damaged myocytes, was clearly observed in some instances where biopsy showed that rejection was present but had not proceeded to the point of visible myocytolysis (*20*).

ACKNOWLEDGMENT

The authors thank the following individuals at the Buffalo Veterans Administration Medical Center for their expert assistance in this study: Drs. J. Bhayana, J. Aldridge, M. A. Abdel-Nabi, M. J. Feldman and T. Spooner, Ms. J. A. Dudkiewicz and Ms. D. Reimers. They also thank Dr. M. E. Billingham, Stanford University, for reading the biopsies of Patient 6 reported in the text.

This work was supported in part by The Veterans Administration Medical Funds and a Merck, Sharp and Dohme International Fellowship in Clinical Pharmacology. Dr. Yamamoto held the Merck Fellowship while on leave from Nagoya University School of Medicine, Nagoya, Japan.

REFERENCES

1. Caves PK, Stinson EB, Billingham ME, Shumway NE. Serial transvenous biopsy of the transplanted human

heart. Improved management of acute rejection episodes. *Lancet* 1974; 1:821–826.
2. Oluwole S, Wang T, Fawwaz R, et al. Use of indium-111-labeled cells in measurement of cellular dynamics of experimental cardiac allograft rejection. *Transplantation* 1981; 31:51–55.
3. McGregor CGA, Hatz R, Aziz S, Billingham ME, McDougall IR. Technetium-99m pyrophosphate in diagnosis of acute cardiac rejection in the rat, with effect of cyclosporine: concise communication. *J Nucl Med* 1984; 25:870–873.
4. Golitsin A, Pinedo JI, Cienfuegos JA, Chamorro JL, Ortiz-Berrocal J, Castillo-Olivares VL. Thallium-201 uptake: a useful method of assessing heart transplantation. *Transplant Proc* 1984; 16:1262–1263.
5. McGregor CGA, Hannan WJ, Wheatley DJ, Smith AF, Muir AL. Radionuclide assessment of myocardial injury in a heterotopic rat heart transplant model. *Int J Nucl Med Biol* 1984; 11:189–194.
6. Fawwaz RA, Iga C, Hardy MA, Alderson PO. Diagnosis of cardiac allograft rejection with indium-111 labeled platelets in cyclosporin treated rats. *J Nucl Med* 1984; 25:80–81
7. Bergsland J, Carr EA, Carroll M, et al. Uptake of myocardial imaging agents by rejected hearts. *J Heart Transplant* 1985; 4:536–40.
8. Pinedo JI, Golitsin A, Cienfuegos JA, Castillo-Olivares JL, Figuera D, Berrocal JO. Role of ^{201} T1 in the management of cardiac transplantation. *Eur J Nucl Med* 1985; 10:203–207.
9. Hall TS, Baumgartner WA, Borkon AM, et al. Diagnosis of acute cardiac rejection with antimyosin monoclonal antibody, phosphorous nuclear magnetic resonance imaging, two-dimensional echocardiography, and endocardial biopsy. *J Heart Transplant* 1986; 5:419–424.
10. Eisen HJ, Eisenberg SB, Saffitz JE, Bolman RM III, Sobel BE. Noninvasive detection of rejection of transplanted hearts with indium-111-labeled lymphocytes. *Circulation* 1987; 75:868–876.
11. Wilson MA, Kahn DR. Scintigraphic assessment of heterotopic cardiac transplants. *Am J Roentgenol* 1981; 137:689–693.
12. McKillop JH, Goris ML. Thallium-201 myocardial imaging in patients with previous cardiac transplantation. *Clin Radiol* 1981; 32:447–449.
13. Nitkin RS, Hunt SA, Schroeder JS. Accelerated atherosclerosis in a cardiac transplant patient. *J Am Coll Cardiol* 1985; 6:243–245.
14. Richter J, Herreros J, Serena A, et al. ^{201}T1 myocardial imaging in a cardiac rejection episode. *Eur J Nucl Med* 1986; 11:368–370.
15. Meneguetti JC, Camargo EE, Soares J Jr, et al. Gallium-67 imaging in human heart transplantation: correlation with endomyocardial biopsy. *J Heart Transplant* 1987; 6:171–176.
16. Silver MA, Grusk BB, Dillehay GL. Gallium-67 scanning is not useful in detecting cardiac allograft rejection. *J Heart Transplant* 1988; 7:65.
17. McKillop JH, McDougall R, Goris MC, Mason JW, Reitz BA. Failure to diagnose cardiac transplant rejection with Tc-99m-PYP images. *Clin Nucl Med* 1981; 6:373–377.
18. Alivizatos PA, Rose ML, Aikenhead J, Pomerance A, Chisholm PM, Yacoub MH. Migration of ^{111}In-labeled autologous leucocytes to the grafts of heart transplant patients. *Transplant Proc* 1985; 17:614–615.
19. Frist W, Yasuda T, Sevall G, et al. Non-invasive detection of human cardiac transplant rejection with indium-111 antimyosin (Fab) imaging. *Circulation* 1987; 76(supp V):V-81–V-85.
20. Carrio I, Berna LL, Ballester M, et al. Indium-111 antimyosin scintigraphy to assess myocardial damage in patients with suspected myocarditis and cardiac rejection. *J Nucl Med* 1988; 29:1893–1900.
21. Billingham ME. Diagnosis of cardiac rejection by endomyocardial biopsy. *Heart Transplant* 1982; 1:25–30.
22. Imakita M, Cohnert TR, Billingham ME. Endocardial infiltrates: the "Quilty" effect. *J Heart Transplant* 1988; 7:57.