Pulmonary Uptake in Indium-111-Antimyosin Fab Fragment Imaging Following Human Cardiac Transplantation

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Recent studies suggest that cardiac uptake of ^{111}In-labeled antimyosin monoclonal antibody may be estimated semiquantitatively by calculating a heart-to-lung activity ratio, with pulmonary uptake serving as a reference region. **Methods:** We obtained 96 ^{111}In-antimyosin scintigraphs to monitor rejection occurrence after heart transplantation in 26 patients. **Results:** On five scintigraphs, the count rate density in ROIs over the lungs was markedly higher (mean 53% higher) than that in the immediately preceding and following scintigraphs, whereas the activity in the heart was essentially unchanged. Four of these scintigraphs coincided with ongoing pulmonary infection and the fifth with an occurrence of a high anti-CMV titer. **Conclusion:** The mechanism of apparent nonspecific antimyosin accumulation in the lungs is uncertain, although increased capillary permeability may be one possibility. Attention should be given to activity in the lungs if this activity is used as a reference in studies of ^{111}In-antimyosin uptake in the heart.

Key Words: cardiac transplantation; ^{111}In-antimyosin Fab fragment; pulmonary uptake

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Measurements of cardiac uptake of ^{111}In-labeled antimyosin antibody have been recommended for detection of allograft rejection after heart transplantation (*1–3*). In such studies, calculation of a heart-to-lung uptake ratio has been used as a semiquantitative measure of antimyosin accumulation in the heart (*4*). A ratio lower than 1.55 at 1 yr after heart transplantation has been suggested as a "safe limit," making future rejection unlikely (*5*). In a series of scintigraphic studies during the first year after heart transplantation, we observed patients with ^{111}In-antimyosin accumulation in the lungs, thus complicating the use of pulmonary uptake as a reference region.

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CASE REPORT

Methodology

We studied 26 patients who had ^{111}In-antimyosin imaging and endomyocardial biopsies at scheduled times after heart transplantation. Ninety-six antimyosin scans were obtained. A planar scintigraphic image in the anterior projection was acquired 48 hr after intravenous injection of 70–90 MBq ^{111}In-monoclonal antimyosin antibody Fab fragments and 24 hr after endomyocardial biopsy. Imaging was performed for 20 min using a gamma camera with a high-resolution medium-energy collimator and 20% windows centered on the 171 and 240 keV peaks. Images were collected in a 256 × 256 matrix and stored for later analysis.

For quantitative evaluation, we calculated a heart-to-lung uptake ratio based on average count rates per pixel in regions of interest (ROIs) over the heart and both lungs, as described by Carrió et al. (*4*). In the analysis of subsequent scintigraphs in the same patient, the previously applied ROIs were transferred to the new scintigram and moved "into place" to obtain ROIs with an identical number of pixels and shape. Our heart-to-lung ratios are generally higher than previously reported because we used somewhat smaller sized cardiac ROIs.

Patients

In one instance (Fig. 1), five patients had a remarkably low heart-to-lung value (range 1.03–1.54) when compared with the stable values from the previous and following studies (range 1.75–2.19). For all patients, the abrupt drop in the heart-to-lung ratio was due to increased uptake in pulmonary ROIs rather than decreased uptake in the cardiac ROI (Table 1). As described below, signs of pulmonary infection were demonstrated when the low heart-to-lung ratio was obtained in four patients and a marked rise in total anti-CMV titer was found in the fifth patient. There were no signs of rejection in any of the 23 endomyocardial biopsies taken at the time of scintigraphy (i.e., 24 hr after isotope injection, 24 hr before imaging).

Patient 1. This patient displayed clinical and roentgenological lung infection coincident with a very marked drop in heart-to-lung ratio 26 wk after heart transplantation. The scintigram at that time showed obvious diffuse activity in the lungs, almost masking the cardiac accumulation evident in the previous and following studies (Fig. 2). Trophozoites of *Pneumocystis carinii* were demonstrated in the broncho-alveolar lavage fluid (BAL) and in lung biopsies, which showed marked interstitial pneumonia. No CMV inclusions were found, although CMV could be cultured from the blood, BAL, urine and saliva. Total anti-CMV titer was negative. The pulmonary diffusion capacity was normal before heart trans-

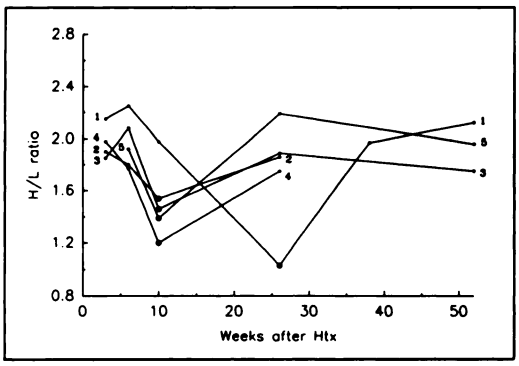

FIGURE 1. Heart-to-lung ratios obtained from ^{111}In-antimyosin scans of five patients at various times after heart transplantation. Patient number is given at the beginning and end of the curves. Filled circles denote occurrence of lung infection (Patients 1, 2, 3, 5) or a marked rise in total anti-CMV titer (Patient 4).

plantation and almost normal 1 yr after heart transplantation, but was reduced to one-third of normal when the low heart-to-lung ratio was calculated. At that time, the patient was clinically ill but recovered gradually after treatment with antibiotics.

Patient 2. This patient displayed clinical lung infection coincident with a moderate drop in the heart-to-lung ratio 10 wk after heart transplantation. The scintigram at this time showed slightly increased pulmonary uptake (Fig. 3). Trophozoites of *Pneumocystis carinii* were demonstrated in moderate numbers in BAL (no biopsies were taken). CMV could be cultured from BAL and saliva but not from blood. Total anti-CMV titer rose from 160 to 1280 and fell again 4 wk later. Clinical recovery was achieved within 1–2 wk.

Patient 3. Clinical and roentgenological lung infection coincident with a moderate drop in the heart-to-lung ratio 10 wk after heart transplantation was observed. The infectious agent was not identified and the patient recovered quickly after treatment with penicillin.

Patient 4. A rise in total anti-CMV titer to more than 3125, coincident with a marked drop in the heart-to-lung ratio 10 wk after heart transplantation was noted. The titer had been 320 and 1280 at 3 and 6 wk and fell again to 640 at 26 wk after heart

TABLE 1
Count Rate Density in ROIs over Heart and Lungs from Indium-111-Antimyosin Scintigraphies in Five Heart Transplant Patients with Abrupt Drops in the Heart-to-Lung Ratio*

Weeks after transplantation	Patient no.				
	1	2	3	4	5
3	67/31	47/25	44/24	46/23	
6	64/28	48/27	35/17	34/19	42/22
10	67/34	47/31†	32/22†	39/32‡	41/29†
26	63/61†	47/25	36/19	27/15	46/21
38	60/30				
52	62/29		29/17		42/22

*The numbers (heart/lung) denote counts/20 min/pixel normalized to a dose of 80 MBq ^{111}In. The average number of pixels in ROIs over heart/lungs was approximately 600/2100 (range 328–1022/1429–3331).
†Occurrence of lung infection.
‡Occurrence of marked rise in total anti-CMV titer.

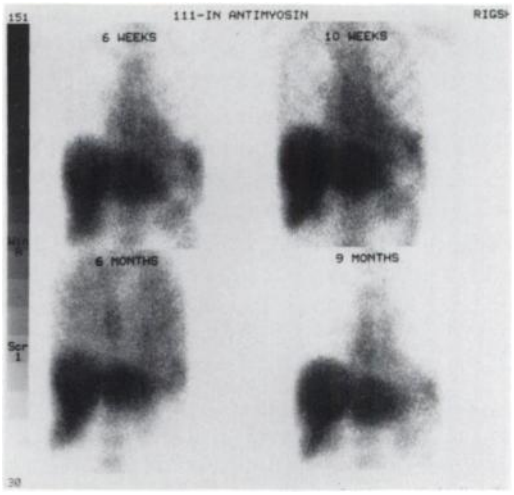

FIGURE 2. Antimyosin scintigrams 6 wk, 10 wk, 6 mo and 9 mo after heart transplantation in Patient 1 demonstrate increased diffuse uptake at 6 mo, where evidence of *Pneumocystis pneumonia* was present.

transplantation. No clinical and roentgenological signs of lung infection were demonstrated and no treatment was given. Lung function tests were normal. The high count rate in the pulmonary ROIs was due to uptake in the ribs rather than in the lung parenchyma. Also, liver uptake was strikingly more prominent on the 10-wk scintigram than on the scintigrams obtained 6 and 26 wk after heart transplantation.

Patient 5. Clinical and roentgenological lung infection coincident with a marked drop in the heart-to-lung ratio 10 wk after heart transplantation was observed. A positive titer against *Legionella jordanis* was demonstrated at the same time. The titer was normal 7 wk later without treatment.

DISCUSSION

Indium-111-labeled monoclonal antimyosin Fab fragment, developed by Haber et al. (*6*) and Khaw et al. (*7*) as

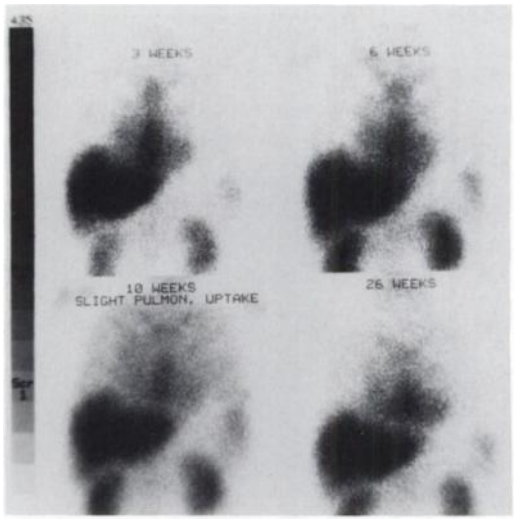

FIGURE 3. Antimyosin scintigrams 3, 6, 10 and 26 wk after heart transplantation in Patient 2 demonstrate slight pulmonary uptake at 10 wk, where evidence of *Pneumocystis pneumonia* was present.

an antibody reacting specifically with cardiac myosin, is taken up by necrotic myocardial cells (*8*), as would be expected if binding requires disrupted cell membranes with exposition of intracellular myosin to the extracellular fluid.

Indium-111-labeled antimyosin has been successfully used to detect not only myocardial infarction (*9*) but also myocarditis (*4*), cardiotoxicity of anthracyclines in patients with malignant disease (*10*) and allograft rejection after heart transplantation (*1–5*). In the latter applications, cardiac uptake is diffuse rather than focal, creating a need for grading or quantification. A visual grading system was first suggested (*2*) followed by a widely accepted, more quantitative approach based on calculation of the ratio between the count rate per pixel in the heart and the supposedly constant count rate per pixel in the lungs. We found, however, sudden, transitory increases in the count rate in pulmonary ROIs in five of 26 patients after heart transplantation; a finding that complicates this approach. Moreover, in some patients, visible pulmonary uptake was so moderate that it could easily be overlooked.

In addition to our findings, there are two other reports of focal nonantigen-specific tissue localization of antimyosin Fab fragment at the site of lung inflammation in a patient with myocardial infarction (*11*) and at tumor sites in 18 of 19 patients with soft-tissue sarcomas (*12*). In the latter report, cardiac myosin was detected by immunocytochemistry in only one of ten tumors tested.

The mechanism of the extracardiac uptake of ^{111}In activity is uncertain. In cases of accumulation of radiolabeled, monoclonal or polyclonal IgG at inflammatory sites in humans and experimental animals, molecule accessibility to the extravascular compartment seems to be of major importance (*13–15*). By analogy, increased capillary leakage may contribute to extracardiac ^{111}In-antimyosin accumulation. The cause of increased activity in the pulmonary ROIs in Patient 4, who had no clinical lung infection but a high anti-CMV titer, may be different. The scintigraphic indication of activity in the ribs and the liver suggests uptake in the reticulo-endothelial system, but the mechanism is still obscure. Two of our 26 patients exhibited signs of pneumonia and one patient had a very high anti-CMV titer without concomitant increase in pulmonary ROI activity.

Apart from uncertainty about the mechanism of radiolabeled antimyosin accumulation in pulmonary ROIs, our findings emphasize the importance of paying attention to such accumulation before a reduced heart-to-lung ratio is taken to suggest low risk of rejection after heart transplantation. Also, scintigraphic evidence of transplant rejection may be overlooked when this occurs concomitant with pulmonary activity accumulation.

REFERENCES

1. Ballesten M, Obrador D, Carrió I, et al. Early postoperative reduction of monoclonal antimyosin antibody uptake is associated with absent rejected related complications after heart transplantation. *Circulation* 1992;85:61–68.
2. Frist W, Yasuda T, Segall G, et al. Noninvasive detection of human cardiac transplant rejection with indium-111-antimyosin (Fab) imaging. *Circulation* 1987;76(suppl V):V81–V85.
3. Johnson LL, Cannon PJ. Antimyosin imaging in cardiac transplant rejection. *Circulation* 1991;84(suppl I):I273–I279.
4. Carrió I, Berná L, 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.
5. Ballester M, Obrador D, Carrió I, et al. Indium-111-monoclonal antimyosin antibody studies after the first year of heart transplantation. *Circulation* 1990;82:2100–2108.
6. Haber E, Katus HA, Hurrell JG, et al. Detection and quantification of myocardial cell death: application of monoclonal antibodies specific for cardiac myosin. *J Mol Cell Cardiol* 1982;14(suppl 3):139–146.
7. Khaw BA, Mattis JA, Mehnicoff G, et al. Monoclonal antibody to cardiac myosin: imaging of experimental myocardial infarction. *Hybridoma* 1984;3: 11–23.
8. Khaw BA, Fallon JT, Beller GA, Haber E. Specificity of localization of myosin-specific antibody fragments in experimental myocardial infarction: histologic, histochemical, autoradiographic and scintigraphic studies. *Circulation* 1979;60:1527–1531.
9. Khaw BA, Yasuda T, Gold HK, et al. Acute myocardial infarct imaging with In-111-labeled monoclonal antimyosin Fab. *J Nucl Med* 1987;28:1671–1678.
10. Carrió I, Estorch M, Berná L. Assessment of anthracycline-induced myocardial damage by quantitative ^{111}In-antimyosin monoclonal antibody studies. *Eur J Nucl Med* 1991;18:806–812.
11. Kumita S, Nishimura T, Vehara T, et al. Accumulation of ^{111}In-antimyosin antibody at the focal site of inflammation. *Jpn J Nucl Med* 1990;27:1439–1442.
12. Kareimo KJA, Wiklund TA, Liewendahl K, et al. Imaging of soft-tissue sarcomas with indium-111-labeled monoclonal antimyosin Fab fragments. *J Nucl Med* 1990;31:23–31.
13. Rubin RH, Fischman AJ, Needleman M, et al. Radiolabeled, nonspecific, polyclonal human immunoglobulin in the detection of focal inflammation by scintigraphy: comparison with gallium-67-citrate and technetium-99m-labeled albumin. *J Nucl Med* 1989;30:385–389.
14. Fischman AJ. When magic bullets ricochet [Editorial]. *J Nucl Med* 1990; 31:32–33.
15. Oyen WJG, Claessens RAMJ, van der Meer JWM, Corstens FHM. Biodistribution and kinetics of radiolabeled proteins in rats with focal infection. *J Nucl Med* 1992;33:388–394.