Indium-111 Antimyosin Scintigraphy to Assess Myocardial Damage in Patients with Suspected Myocarditis and Cardiac Rejection

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Indium-III antimyosin scans were used to assess myocardial damage in patients with suspected myocarditis and cardiac transplant rejection. The calculation of a myocardium to lung ratio (AM index) to quantify antimyosin uptake was performed. AM index in normal subjects (n = 8) at 48 hr postinjection was 1.46 ± 0.04. In patients with suspected myocarditis (16 studies in 13 patients), AM index was 2.0 ± 0.5 ($p < 0.001$); suggesting a considerable incidence of ongoing cell damage in this group, despite the small proportion of positive right ventricular endomyocardial biopsy (RVbx) (4/13). In patients studied after cardiac transplantation (37 studies in 17 patients), AM indexes correlated with RVbx. In patients with RVbx proven rejection (n = 14), AM index was 1.87 ± 0.19 ($p < 0.001$). In patients with RVbx showing infiltrates but not myocyte damage (n = 13), AM index was 1.80 ± 0.27 ($p = 0.02$). In patients with normal RVbx (n = 10), AM index was 1.56 ± 0.17 (p = NS versus controls; $p = 0.001$ versus those with positive RVbx). Calculated AM indexes correlated with graded visual analysis of the scans ($r = 0.823$; $p = 0.001$). Antimyosin scans are an appropriate method to assess myocardial damage in patients with suspected myocarditis and cardiac rejection.

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Indium-111 antimyosin (^{111}In) specifically binds to exposed cardiac myosin and has been successfully used to precisely delineate myocardial necrosis in patients with myocardial infarct (*1,2*). The usefulness of such an antibody to detect myocardial cell damage in other pathologic entities such as myocarditis and cardiac rejection has been suggested (*3,4*).

Active myocarditis and cardiac rejection are both characterized by the production of inflamatory infiltrates adjacent to necrotic or degenerative myocytes, with or without interstitial fibrosis (*5,6*). It is likely that antimyosin scans could identify myocardial cell damage in such situations by the well known mechanism of binding to myosin exposed to extracellular fluid by loss of cell membrane integrity.

In our institution, a referral center for cardiac transplantation, patients with myocarditis are investigated as potential transplant candidates. Identification of active myocarditis is important as these patients can potentially benefit from immunosuppressive therapy (*7*). The gold standard to diagnose myocarditis remains right ventricular endomyocardial biopsy (RVbx), a method which can lack sensitivity due to sampling error (*7*). Diagnosis of active myocarditis is still made by clinical symptoms, and decisions regarding therapy are often taken without a positive RVbx. There is, therefore, a need for a test that can document the extent of myocardial damage in these patients.

The follow-up of patients after cardiac transplantation is a major clinical concern, especially during the first year postsurgery, when the occurrence of cardiac rejection is more frequent (*8,9*). Diagnosis of cardiac rejection is made by analysis of RVbx performed sequentially after surgery. The basic variable used for the diagnosis of cardiac rejection and its subsequent control is the pathologic identification of myocardial cell damage. In these patients, the severity of cardiac rejection observed in the RVbx determines the subsequent degree of immunosuppression therapy. Due to the very high

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TABLE 1
Results of Antimyosin Studies and RVbx in Patients Suspected of Having Myocarditis

Patient no.	Age (yr)	Sex	LVEF*	Visual score	AM† index†	RVbx‡
1a	19	M	17%	2	1.78	—
1b			20%	2	2.10	—
1c			30%	1	1.40	—
1d			26%	1	1.67	—
2	27	M	20%	0	1.70	—
3	52	M	38%	3	1.90	—
4	42	M	24%	3	2.80	—
5	37	M	15%	2	2.60	—
6	46	F	16%	2	1.76	+
7	34	F	18%	1	1.50	—
8	40	M	20%	2	2.16	+
9	35	M	31%	2	2.22	—
10	49	M	23%	2	1.89	+
11	50	M	33%	2	3.03	+
12	39	M	20%	2	2.0	—
13	31	M	31%	0	1.5	—

* Left ventricular ejection fraction.
† Antimyosin index of uptake, expressed as a myocardium to lung ratio.
‡ Endomyocardial biopsy positive or negative for the disease.
Studies performed consecutively on the same patient indicated as a, b, c, d.

cost of sequential RVbx, there is a clear need for non-inversive diagnostic alternatives. This study has been undertaken to assess the ability of antimyosin scans to demonstrate diffuse myocardial damage in patients with suspected myocarditis and rejection after cardiac transplantation.

MATERIALS AND METHODS

Subjects

A control group of eight healthy male volunteers, aged 32 yr (range 28–38 yr) were selected after normal physical examination, chest x-ray, electrocardiogram, and two-dimensional echocardiogram.

Thirteen patients suspected of having myocarditis, 11 men, 2 women, aged 39 yr (range 19–50), diagnosed either by RVbx or clinical symptoms, were studied (Table 1). All patients presented with global left ventricular dysfunction demonstrated by equilibrium-gated blood-pool scanning at the time of the study. The average left ventricular ejection fraction in this group was 24% (range 16–38%). Heart failure was present for < 6 mo in ten patients and presented as acute onset in three. One patient (No. 6) had a previous episode of biopsy-proven myocarditis, and presented with symptoms of relapse. Three patients presented with a febrile, virus-like illness before the development of cardiac symptoms. Pericarditis was present in four patients. Sixteen studies were done in this group, with a maximum of four studies in 9 mo in one patient.

Seventeen patients, 14 men and 3 women, aged 39 yr (range 19–52 yr), were studied 7 days to 30 mo (mean 7 mo) after orthothopic cardiac transplantation (Table 2). Immunosuppression after transplantation was based on the administration of cyclosporine and steroids. Antithymocytic globulin was given prophylactically for 10 days after transplantation. Cyclosporine doses were adjusted to attain whole blood levels between 400–800 ng/ml. Steroids were given in the form of bolus of methylprednisolone, 1 g, 500 mg, and 500 mg for the

TABLE 2
Results of Antimyosin Studies and RVbx in Patients with Cardiac Transplant

Patient No.	Age (yr)	Sex	Visual score	AM* index	RVbx† score
1	39	M	2	2.20	3
2a	42	F	3	2.40	0‡
2b			2	1.85	3
2c			1	2.50	1
2d			1	1.77	3
2e			1	1.75	1
3	43	F	2	2.0	2
4	25	M	1	1.47	0§
5a	52	M	2	1.70	3
5b			1	1.66	3
5c			1	1.53	1
6a	49	M	1	1.66	3
6b			1	1.70	1
6c			1	1.60	3
6d			1	1.70	1
6e			2	1.68	1
7	45	M	2	1.77	1
8	40	F	2	2.0	1
9a	35	M	3	2.0	3
9b			3	1.83	3
9c			3	2.0	3
10a	27	M	1	1.40	0
10b			2	1.80	1
10c			2	1.70	1
11	49	M	3	2.12	3
12a	42	M	2	2.0	0‡
12b			1	1.60	0
12c			0	1.30	0§
13a	19	M	1	1.80	0
13b			1	1.65	0
14a	46	M	3	2.0	3
14b			3	1.80	3
14c			1	2.0	3
15	39	M	1	1.72	0
16a	46	F	3	1.80	0
16b			1	1.45	0
17	26	M	2	1.60	0§

* Antimyosin index of uptake, expressed as a myocardium to lung ratio.
† Endomyocardial biopsy score as: 0, i.e., normal specimens; 1–2, infiltrates but without myocyte lysis; and 3, infiltrates with myocyte lysis.
‡ Studies performed immediately after transplantation (first week).
§ Studies performed after the first year post-transplantation.
Studies performed consecutively on the same patient indicated as a, b, c, . . .

first 3 days after transplantation, followed by 1 mg/kg/day of prednisone and a progressive reduction to 0.2 mg/kg/day. Treatment for acute rejection was carried out whenever moderate or severe rejection was detected at RVbx, and consisted of a 3-day course of high dose i.v. methyl-prednisolone (1 g, 500 mg, and 500 mg, respectively) and antithymocytic globulin (initial 5 mg/kg/day and subsequent adjustment to attain a T-cell level between 100–200 mm3). Thirty-seven studies were done in this group, with a maximum of five studies within 5 mo in two patients during different episodes of rejection. RVbx always was performed within an interval of 48 hr of antimyosin injection in this group of patients.

Patients with repeated antimyosin injections were evaluated for the presence of human antimurine antibodies.

Procedure

After giving their informed consent, patients and subjects were injected intradermally with 0.1 ml of the labeled antibody. If no wheal was observed within 30 min, patients were injected intravenously with 0.5 mg of R11D10-Fab-DTPA (Centocor Europe, Leiden, The Netherlands) labeled with 2 mCi of indium-111 (^{111}In).

Planar scintigraphic images were obtained at 24, 48, and 72 hr in anterior and left anterior oblique projections, using a conventional large field-of-view camera with a high resolution medium-energy collimator, 20% window centered on 247 and 173 keV peaks. A minimum of 500,000 counts, between 5 to 10 min, were collected. Analog and digital images collected in a 128/128 matrix were stored for subsequent analysis.

All studies were first inspected visually to determine if there was antimyosin uptake in the myocardium. Visual analysis, to assess the presence or absence of pathologic antimyosin uptake in the myocardium, was done by consensus between three observers blinded to the clinical situation and RVbx results. A four-step score was used: 0, no uptake; 1, mild or faint uptake; 2, clear but moderate uptake; and 3, intense myocardial uptake. To calculate an index of antimyosin uptake (AM index), the digital unprocessed anterior projection at 48 hr was used, adjusting a region of interest (ROI) in the myocardium and a ROI in each lung. Lung regions were drawn as extensively as possible, but avoiding the sternum, bone structures of the shoulder, and the liver (Fig. 1). Average counts/pixel in the myocardium were divided by average counts/pixel in the lungs to obtain the final index of antimyosin uptake.

In the control group, AM index was first calculated on the 24-hr image, using the cardiac pool, which always was visually apparent at that time, as a reference to adjust the cardiac region. The same ROI then was used on the 48- and 72-hr images.

To assess the inter- and intraobserver variability of the calculation of the index of antimyosin uptake, all studies were reviewed at random and the quantifications repeated by two independent observers, twice, at separate intervals.

RVbx were performed using a Cordis bioptome, obtaining four to eight samples from the right ventricle at each procedure and were processed by light microscopy. Biopsy scores in patients with cardiac transplantation were: 0, i.e., normal specimens; 1, mild interstitial infiltrates; 2, moderate to important interstitial infiltrates but without myocyte lysis; and 3, infiltrates with clear myocyte lysis. Biopsies of patients with suspected myocarditis were interpreted as positive or negative for the disease, following the Dallas criteria (*5*).

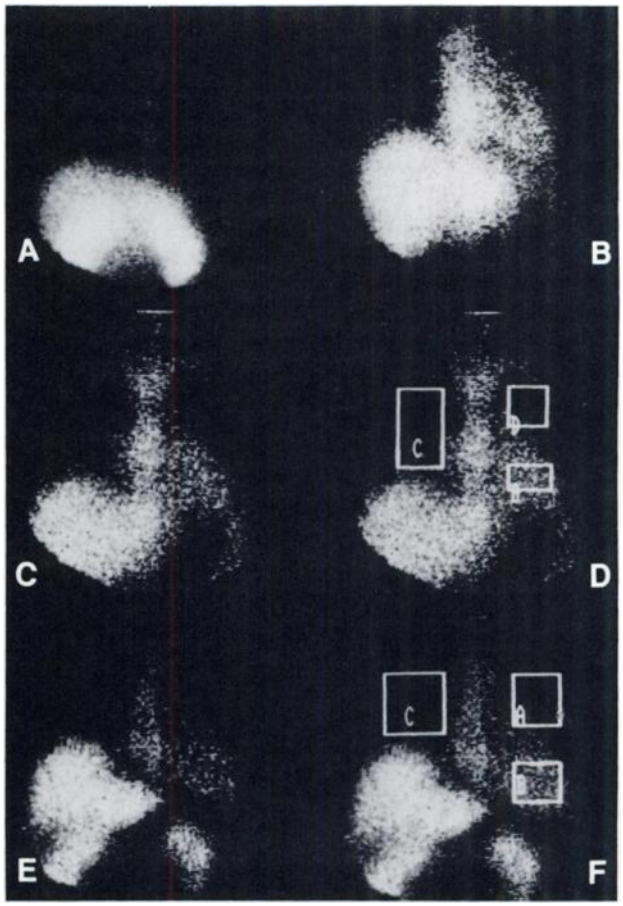

FIGURE 1
Antimyosin scans. A: Normal subject 48 hr postinjection; visually negative study. B: Patient with RVbx positive for rejection (No. 11); visually positive study. C: Patient with RVbx proven rejection (No. 9a); visual score 3. D: ROIs used to calculate AM index in the patient in panel C; AM index 2.0. E: Patient with myocarditis (8); visual score 2. F: regions of interest used to calculate AM index in the patient in panel E; AM index 2.16.

Statistical Analysis

Normal distribution of values within groups was assessed using the Kolmogorov-Smirnov test. Differences between groups of patients and subjects were compared using the two-sample t-test. Comparison of index values in controls at 24, 48, and 72 hr were performed by a one-way analysis of variance. Comparison between visual scores and quantified indexes was assessed by linear regression analysis. An observed significance level smaller than 0.05 was required to consider the statistical analysis significant.

RESULTS

Skin tests were negative in all control subjects and patients. Human antimurine antibodies were undetected in patients with repeated injections.

Control Subjects

In the control group, the cardiac blood pool was always apparent at 24 hr (visual score, 1–2), with a cardiac to lung ratio of 1.71 ± 0.13 (Fig. 2). At 48 hr, all studies in this group were visually negative (visual score, 0) and cardiac-to-lung ratio was 1.46 ± 0.04 ($p < 0.001$) (Fig. 2). At 72 hr, all studies remained visually negative and cardiac-to-lung ratio was again 1.46 ± 0.13 (Fig. 2). The same plateau in the pattern of uptake was observed in patients, therefore, values obtained at 48 hr postinjection were used for analysis and comparison between groups.

Patients with Suspected Myocarditis

In the group of patients with suspected myocarditis, the index of antimyosin uptake was 2.0 ± 0.5 ($p <$ 0.001 versus normals) (Table 1, Fig. 3). Visual scores correlated with calculated AM indexes. Patients with visual scores of 0–1 (n = 5) had a mean AM index of 1.54 ± 0.11 (range 1.5–1.7); patients with visual scores of 2–3 (n = 11) had a mean AM index of 2.17 ± 0.44 (range 1.76–3.03) ($p = 0.001$). RVbx was positive for myocarditis in only four patients (Table 1), all of whom had visually positive AM studies (score of 2) and AM indexes ranging from 1.76 to 3.03.

Patients with Cardiac Transplantation

In the group of patients studied after cardiac transplantation, the index of antimyosin uptake was 1.79 ± 0.3 (n = 37) (Table 2, Fig. 3). If only studies with definitive RVbx for rejection (score 3) were included (n = 14), the mean AM index was then 1.87 ± 0.19. Both values were significantly different than those of controls ($p < 0.001$), and the index in patients with biopsy proven rejection was not significantly different than of patients with suspected myocarditis and positive AM scans. Studies with RVbx of score 0 had a mean index of AM uptake of 1.68 ± 0.29. If we excluded from this group the first studies of Patients 2 and 12, who were studied immediately after surgery, the AM index was then 1.56 ± 0.17 (p = N.S. versus controls; $p = 0.001$ versus the group with RVbx score of 3). Studies with RVbx score of 1–2 had a mean index of antimyosin uptake of 1.80 ± 0.27 ($p = 0.02$ versus studies with RVbx score of 0, and p = N.S. versus studies with RVbx score of 3) (Fig. 4). Visual scores in this group correlated with calculated AM indexes. Studies with visual score of 0–1 (n = 18) had a calculated AM mean index of 1.65 ± 0.26 (range 1.3–2); studies with visual scores of 2–3 (n= 19) had a calculated AM index of mean 1.90 ± 0.2 (range 1.6–2.5; $p = 0.005$).

Calculated indexes of antimyosin uptake correlated with visual analysis ($r = 0.823$; $p = 0.001$) (Fig. 5). Studies with a visual score of 0 (n = 11) had an index of 1.43 ± 0.11; studies with a visual score of 1 (n = 20) had an index of 1.65 ± 0.25 ($p = 0.003$); studies with a visual score of 2 (n = 20) had an index of 1.96 ± 0.34 ($p = 0.002$); studies with a visual score of 3 (n = 10) had an index of 2.06 ± 0.31 (p = NS) (Fig. 6). Intraobserver variability, when reviewing studies randomly at different times, was 2.27%. Interobserver variability (two observers) was 5.68%. Differences in values obtained intra- and interobservers followed a normal distribution ($p = 0.831$, Kolmogorov test). When comparing differences in values obtained between Observer 1 and 2, the p value was 0.929.

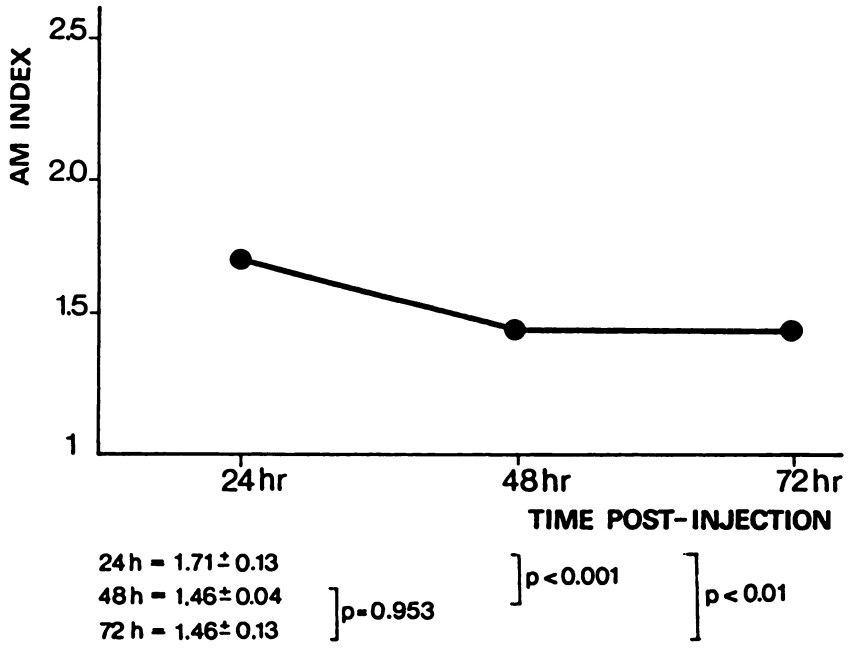

FIGURE 2
Calculated AM indexes in normal subjects, at 24, 48, and 72 hr postinjection. The higher value observed at 24 hr appears to correspond to a larger proportion of circulating antibody (intravascular activity) at this time.

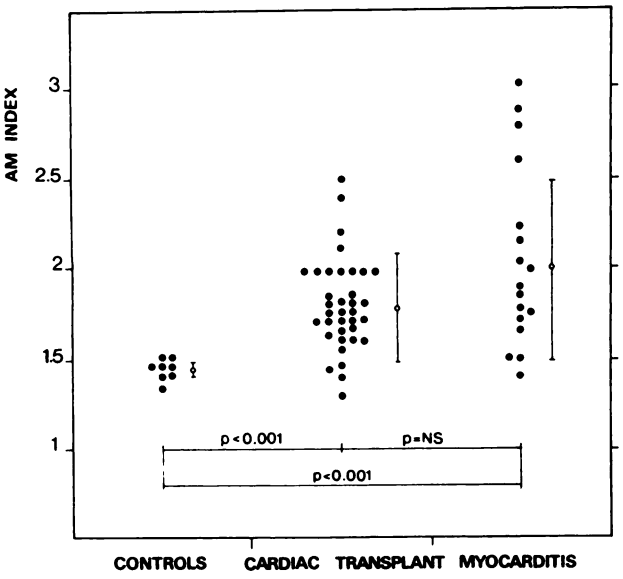

FIGURE 3
Calculated AM indexes in the different groups studied.

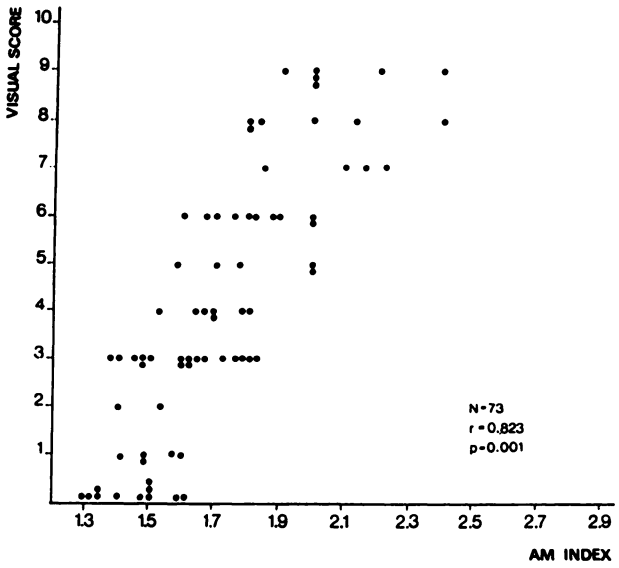

FIGURE 5
Comparison of calculated AM indexes to visual analysis. For this comparison, visual values were obtained by adding the individual scores (from 0 to 3) of the three observers (i.e., for a study scored 2, 2, 3 the final visual score is 2, but the value used for this comparison is 7). A significant correlation (p = 0.001) was found between calculated AM indexes and visual scores. N = 73; r = 0.823.

DISCUSSION

Antimyosin has been demonstrated to specifically bind to cardiac myosin exposed to extracellular fluid after membrane disruption (*10*). In myocardial infarct, antimyosin scintigraphy has proven to be the best method to delineate in vivo areas of myocardial necrosis (*2*). From a theoretical point of view, antimyosin scintigraphy seems an appropriate method to evaluate the extent and severity of cell damage in pathologic entities such as myocarditis and cardiac rejection, as cell necrosis is present in variable degrees in both situations (*5*, *6*). Prior studies on myocarditis and cardiac rejection (*3*,*4*) have used the visual interpretation alone to classify studies as positive or negative for the disease. There is, however, a need for a quantification of myocardial AM uptake in these patients, because changes in the degree of AM uptake could document either improvement or worsening of the disease, or could assess the response to immunosuppressive therapy.

Scintigraphic antimyosin studies at 24 hr postinjection in normal subjects usually show visually apparent mild cardiac blood-pool activity, which tends to disappear at 48 hr. This finding agrees with the described

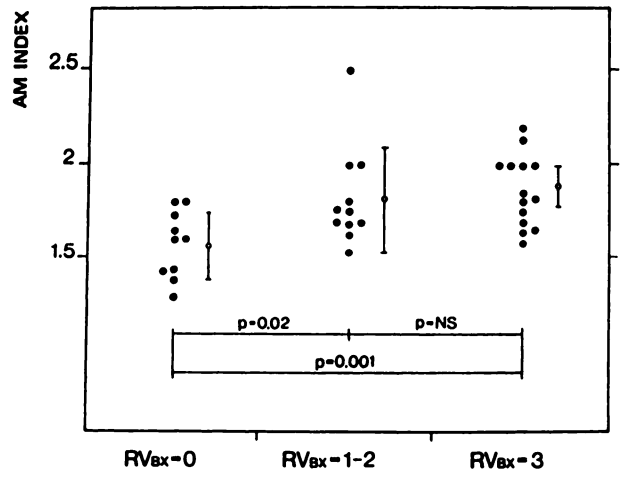

FIGURE 4
Calculated AM indexes in patients studied after cardiac transplantation (excluding studies 2a and 12a, which were done immediately after surgery), compared to RVbx scores.

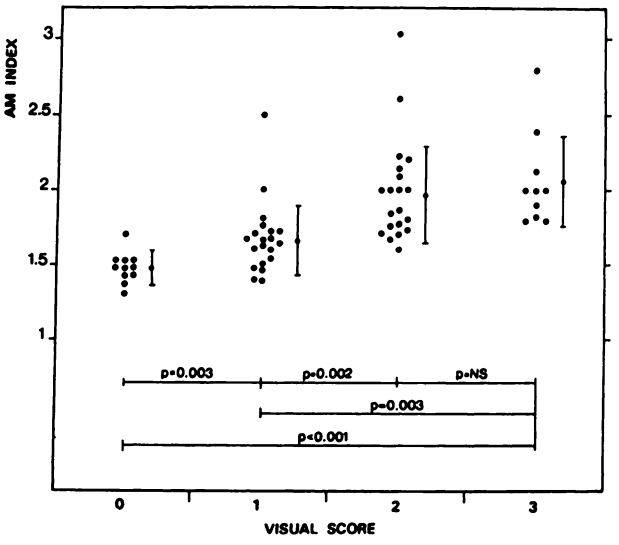

FIGURE 6
Calculated AM indexes compared to visual scores (from 0 to 3) for all studies.

half-life of 4 to 6 hr of antimyosin in blood (*1*). Blood-pool activity at 24 hr in antimyosin scans has not been found to be a problem when delineating myocardial infarcts (*2*), but can be a problem when studying diffuse disease. More delayed images have been suggested by Yasuda et al. (*3*) to study antimyosin uptake in patients with myocarditis. Patients studied at 24 hr postinjection in our series also presented with apparent blood-pool activity but this disappeared at 48 hr; images obtained at 72 hr in the same patients did not show a different heart to lung ratio. Only one patient with cardiac transplantation who had renal insufficiency presented with persistent high blood-pool activity and was excluded from the study. In view of our data, to standardize interpretation of antimyosin scans in myocarditis and cardiac rejection, the 48-hr scan is the appropriate choice.

Visual analysis of antimyosin scans at 48 hr postinjection in patients with myocarditis or cardiac rejection presents no special difficulties. If the anteroposterior projection suggests mild diffuse uptake but residual blood pool is still a concern, an oblique projection helps to identify uptake in the myocardial wall (Fig. 7).

To quantify myocardial antimyosin uptake we chose a myocardium to lung ratio because other surrounding regions of comparison presented important problems. The comparison to liver uptake did not seem adequate because the proportion of Fab fragments metabolized by the liver is not supposed to be constant (*11*). Bone marrow uptake in the sternum was also variable in our experience. Lung activity, mainly due to circulating antibody, seems the appropriate reference. We used two extensive lung areas. In our experience the use of a unique area on the left lung, especially if it is a small one, significantly underestimates lung activity. The use of two large lung areas allowed an average estimation of lung activity. Keeping the lower limit of the right lung region at least two pixels from the nearest liver region (Fig. 1), avoids the inclusion of significant scatter from liver activity which would produce an overestimation of activity in the lung. The cardiac region also had to be as extensive as possible, but avoid surrounding structures. Using this approach the quantification of the myocardial AM index has been highly reproducible in our hands, as shown in the variability analysis.

In the group of patients with dilated cardiomyopathy and suspicion of myocarditis, the high incidence of visually positive antimyosin scans (11/16) and the incidence of high AM indexes of uptake (11/16; index>1.6) suggest a considerable incidence of ongoing cell damage in this group, despite the small number of biopsy proven myocarditis (4/13). This could be caused by the failure of RVbx to sample sufficient myocardial sites (*12*). We recently have reported that sensitivity of RVbx in the diagnosis of myocarditis in dilated cardiomyopathy (through comparison of preoperative RVbx and the excised heart after transplantation) is as low as 17% (*13*). Similar results to ours have been reported by Yasuda et al. (*3*) when comparing RVbx to antimyosin scans in patients with suspected myocarditis. In this series 8/17 patients with positive scans did not show histologic evidence of myocarditis. This suggests a superior sensitivity of antimyosin scans compared to RVbx in the detection of myocardial damage in these patients.

Longitudinal studies are required to assess the value of pathologic antimyosin myocardial uptake that returns to normal in the follow-up of patients with suspected myocarditis treated by immunosuppression. At present a negative RVbx does not exclude myocarditis, but a positive antimyosin scan strongly suggests active myocarditis or at least an active process in the myocardium producing myocyte damage.

The use of radiolabeled antimyosin antibodies to detect cardiac rejection after cardiac transplantation was first suggested by Khaw et al. (*14*). Recent work in animal models by LaFrance et al. (*15*) and Aldonizio et al. (*16*) strongly suggest that antimyosin antibody

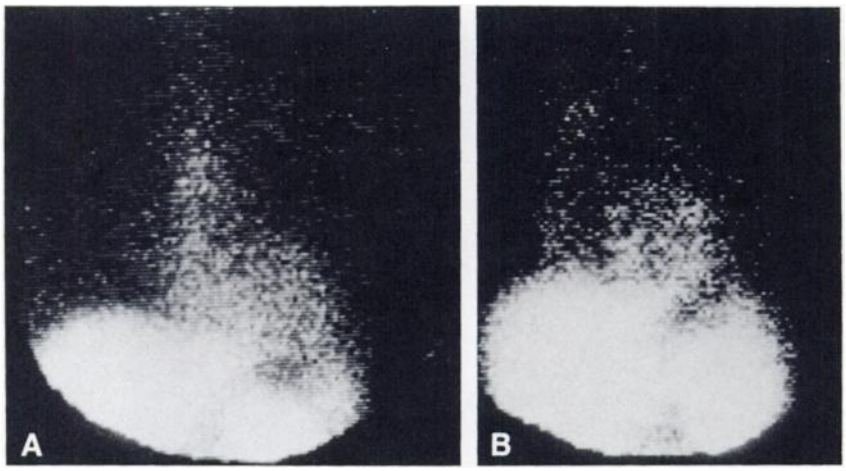

FIGURE 7
Antimyosin scan in a patient with suspected myocarditis (1a). A: Anterior view showing diffuse cardiac uptake. B: Left anterior oblique view, which helps to identify uptake as corresponding to the myocardial wall.

uptake correlates with RVbx scores and can provide a noninvasive method to detect allograft rejection. In cardiac transplantation, rejection activity is enhanced early after surgery; after the graft has escaped the initial acute phase of rejection reactions, a cumulative unresponsiveness to the graft tends to develop as the recipient is continually exposed to the donor antigens (*17*). This is shown during follow-up by the progressive decrease in the percentage of biopsies showing cell damage as a result of the rejection process (*17*). Therapeutic strategy in these patients has to be in relationship to the severity and extent of myocardial damage (*18*). To evaluate myocardial damage with antimyosin scans in these patients, a graded approach using a quantified index seems appropriate.

Our study shows that diffuse antimyosin uptake is frequently present in patients after cardiac transplantation, especially during the first year. Antimyosin scans correlate with RVbx, but antimyosin scans can be visually positive with indexes of uptake of >1.6 in the presence of a RVbx showing inflamatory infiltrates but not clear myocyte necrosis. In our study, only three patients presented with high AM indexes and completely normal RVbx (score 0): Patients 2 and 12 were studied immediately after cardiac transplantation, when myocardial damage due to cardiac transport, manipulation, and reperfusion during surgery can occur; Patient 16, with an index of 1.8 was kept only on low doses of Cyclosporin, and a new index calculated 1 mo later was of 1.45 with RVbx again of score 0.

The two patients who presented with an uneventful clinical course (12 and 16) showed an initially high AM index, which decreased to normal values. The two patients showing a persistently high AM index (9 and 14) both suffered heart failure from rejection; one died, and the other required retransplantation. The three patients (4, 12c, and 17) in follow-up 1 yr postcardiac transplantation presented with low indexes of antimyosin uptake and negative RVbx. As shown in Table 2, these patterns of evolution are better seen with AM indexes than with the visual estimation alone. According to our results, it seems possible that patients after the first year postcardiac transplantation who are doing well and have low indexes of antimyosin uptake can avoid RVbx if AM indexes do not rise.

A major problem seems to be the short range in which AM indexes oscillate. We have no patients with RVbx scores of 3 (definitive myocyte necrosis) and a visually negative scan or an index <1.6. The average value in these patients is 1.87, but longitudinal data still are required to assess the prognostic value of the decrease in AM index uptake.

We have not found detectable human antimurine antibodies in patients with repeated injections. At present we have not studied any one patient more than five times, but if more frequent antimyosin injection can produce the apparition of human antimurine antibodies, this could be a serious limitation for the use of AM scans in long-term follow-up.

In conclusion, diffuse antimyosin uptake in the myocardium is the usual finding when studying patients with suspected myocarditis and rejection after cardiac transplantation. Such diffuse uptake can be observed even in the presence of a negative RVbx, suggesting myocardial damage not detected by the RVbx. We introduce the calculation of a myocardium-to-lung index to express the degree of antimyosin uptake. This index correlates with RVbx scores and with visual analysis and is probably in relationship to the extension and severity of myocardial damage. Longitudinal studies are required to establish the yield of antimyosin scans in follow-up after cardiac transplantation and in the control of response to therapy in patients with myocarditis.

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