Indium-111–Monoclonal Antimyosin Antibody Studies After the First Year of Heart Transplantation

Identification of Risk Groups for Developing Rejection During Long-term Follow-up and Clinical Implications

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The long-term clinical course and results of biopsies in 21 patients studied with monoclonal antimyosin antibodies more than 12 months after heart transplantation according to the presence and degree of antimyosin-antibody uptake is described. Eighteen men and three women aged 20–52 years (39±9 years) were studied with antimyosin antibodies 12–40 months (mean, 22±9 months) after heart transplantation, and followed for a mean of 18 months (10–28 months). The number of biopsies performed during follow-up was 102. Results showed normal antimyosin-antibody studies in nine patients and abnormal studies in 12 patients. Myocyte damage was identified in 18 of the 102 biopsies (17.6%), one in the normal antimyosin-antibody group of patients and 17 in those patients with myocardial antimyosin-antibody uptake. Patients who developed rejection comprised 11% and 67% of each respective group; the mean number of rejection episodes per patient was 0.11±0.33 and 1.41±1.41, respectively (p<0.01). A trend was noted by which higher heart-to-lung ratios were associated with greater probability of rejection. Conclusively, 1) antimyosin-antibody studies performed after more than 1 year after heart transplantation indicate the presence and level of rejection activity, 2) groups of patients at risk for developing rejection at biopsy during long-term follow-up may be detected by antimyosin-antibody study, and 3) surveillance for rejection and the degree of immunosuppression should be tailored to meet individual patient needs. (Circulation 1990;82:2100–2108)

Monoclonal antimyosin antibodies labeled with indium-111 allow in vivo noninvasive detection of myocardial damage. Binding of these antibodies to intracellular myosin takes place only when sarcolemmal disruption occurs and the cell is irreversibly damaged.1–4 This technique has been useful in the diagnosis of acute myocardial infarction5 and acute myocarditis,6 and the detection of active myocyte damage in chronic dilated cardiomyopathy.7 After heart transplantation, antimyosin studies have been used to detect rejection8,9 where conventional diagnostic criteria is based on the morphological identification of myocyte damage at endomyocardial biopsy.10

We have recently developed a means to quantify the relative myocardial uptake of 111In–monoclonal antimyosin antibodies in humans through a heart-to-lung ratio,11 and have shown that after heart transplantation, sequential studies performed in individual patients provide an insight into the level and changes in rejection activity.8 Shortly after transplantation, high antimyosin uptake is invariably detected, and a gradual reduction in the degree of uptake in subsequent months is seen. After the first year, one group of patients show a normal antimyosin study, whereas persistent myocardial uptake is seen in others. No information on the long-term significance of antimyosin studies performed at this time after surgery is available.

The present report provides the first description of the significance of antimyosin studies performed after the first year after transplantation in terms of the probability for developing subsequent rejection at biopsy during long-term follow-up.

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Supported by the “Fondo de Investigaciones Sanitarias de la Seguridad Social” (FISS), Grant nos. 87/0943, 88/0824, and 89/0722.

Received January 5, 1990; revision accepted July 31, 1990.
Methods

Only those patients who had received an orthotopic heart transplantation at least 1 year before the antimyosin study were included. Time elapsed from transplantation to antimyosin study ranged from 12 to 40 months (22±9 months). There were 21 patients, 18 men and three women, aged 20–52 years (39±9 years). Follow-up after antimyosin extended from 10 to 28 months (18±5 months). The total number of biopsies performed during this interval was 102, that is, three to eight (4.8±1.6) biopsies per patient.

Immunosuppression and Management of Rejection

Immediately after transplantation, immunosuppression consisted of the administration of cyclosporine and steroids. Equine antithymocytic globulin (ATGAM) was given for 10 days after transplantation. Cyclosporine doses were adjusted to whole blood levels of 400–800 ng/ml. Steroids were given in the form of a bolus of methylprednisolone, 1 g, 500 mg, and 500 mg for the first 3 days, followed by 1 mg/kg/day of prednisone and reduction to 0.2 mg/kg/day. Endomyocardial biopsies were performed weekly during the first month, every 15 days to the first 3 months, monthly until 6 months, and every 3 months until the first year. After the first year after the transplantation, biopsies were performed every 4 months; three to five samples were taken in each procedure. Azathioprine was given to two patients at a dose of 3–5 mg/day to attain a total leukocyte blood count of 3,000–5,000 mm³.

Diagnosis of rejection was made by interpretation of endomyocardial biopsies according to Billingham’s diagnostic criteria. For the purpose of the present study, the term rejection episode was equated with a biopsy showing myocyte damage (moderate to severe rejection). Treatment was given whenever myocyte damage was detected, but not when round cell infiltration (mild rejection) was the sole finding, and consisted in a 3-day course of an intravenous bolus of methylprednisolone (1 g, 500 mg, and 500 mg) and antithymocytic globulin (5 mg/kg/day and further adjustment to a T-cell level of 100–200 mm³). Control biopsies performed after a rejection episode were excluded from the analysis. Surveillance for vascular rejection was undertaken every 4 months through exercise TI-201 studies and yearly with coronary angiography. We have recently described that when detected at early stages, reversal of small- or medium-sized coronary vessel obstruction with medical treatment is possible. When a positive TI-201 study developed and pruning of the small- and medium-sized coronary vessels was detected, treatment was started with a high-dose bolus of methylprednisolone and antithymocytic globulin.

Left ventricular function was studied at the end of follow-up by means of M-mode and two-dimensional echocardiography.

Antimyosin Studies

Antimyosin administration was made to coincide with endomyocardial biopsies. The Fab fragments of R11D10-Fab-diethylentriamine pentaacetic acid (R11D10-Fab-DTPA) monoclonal antimyosin antibodies (Centocor) were prepared in individual doses to which 2 mCi of 111In-chloride was added to produce a 90% labeling efficacy at room temperature. Patients were injected intradermally with 0.1 ml of the labeled antibody to test for hypersensitivity. If no weal was observed, a dose of 0.5 mg of R11D10-Fab-DTPA labeled with 2.0 mCi of 111In was administered intravenously. All patients presented a negative intradermal test at 30 minutes. Planar scintigraphic images were obtained at 48 hours after antimyosin administration. Imaging was performed in anterior projection by using a conventional large field-of-view camera with a high-resolution medium-energy collimator and 20% window centered on 247 and 173 KeV peaks. A minimum of 500,000 counts between 5 and 10 minutes were collected. Analog and digital images collected in a 128×128 matrix were stored for subsequent analysis.

To quantify the degree of uptake, an experienced observer, unaware of the clinical or biopsy results, calculated an index by dividing average counts per pixel in a cardiac region of interest by those obtained in a pulmonary region of interest. The quantitative criterion for normality was set to a heart-to-lung ratio of 1.55, calculated on the basis of the mean plus two standard deviations of that obtained in a normal population. To maximize the difference between the high and low antimyosin uptake groups, the cutoff point between different degrees of positive antimyosin studies in patients with heart transplantation (low- and high-uptake groups) was arbitrarily set at 1.75, after visual inspection of a plot between the number of rejection episodes per patient detected during follow-up and the heart-to-lung ratios.

Statistical Analysis

The Kolmogorov test was used to check for normal distribution of antimyosin ratio and rejection episodes during the study period. Results suggested that nonparametric tests should be used (Kruskal-Wallis one-way analysis of variance and Mann-Whitney U Wilcoxon sum W test).

A comparison was undertaken between the rejection activity detected during the study with that obtained in the same patients during their first year after transplantation. To allow comparison between these two different intervals, the percentage of positive biopsies detected in each period was normalized by the number of months of the corresponding interval. Thus, the following two variables were calculated: P1 is the biopsies showing rejection divided by the number of biopsies during the first year divided and by the product of 12 and 100 (percentage of positive biopsies per month during the first year), and P2 is the positive biopsies divided by the number.
TABLE 1. Clinical and Antimyosin Data in Patients Evaluated More Than 12 Months After Transplantation and Correlation With Rejection Detected at Biopsy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Months postoperatively</th>
<th>Months follow-up</th>
<th>HLR</th>
<th>BX</th>
<th>Rejection (*)</th>
</tr>
</thead>
</table>
| Patients with normal antimyosin scans
| 1       | M   | 40  | 40                     | 18               | 1.30| -  | No (0)       |
| 2       | M   | 42  | 32                     | 19               | 1.40| -  | No (0)       |
| 3       | M   | 47  | 33                     | 16               | 1.45| -  | No (0)       |
| 4       | M   | 52  | 30                     | 12               | 1.40| -  | No (0)       |
| 5       | M   | 25  | 14                     | 26               | 1.47| -  | Yes (1)      |
| 6       | M   | 46  | 21                     | 17               | 1.50| -  | No (0)       |
| 7       | M   | 39  | 25                     | 10               | 1.40| -  | No (0)       |
| 8       | M   | 43  | 12                     | 12               | 1.35| -  | No (0)       |
| 9       | M   | 20  | 12                     | 12               | 1.50| -  | No (0)       |

Patients with abnormal antimyosin scans
| 10      | M   | 29  | 33                     | 21               | 1.60| -  | Yes (1)      |
| 11      | F   | 44  | 33                     | 16               | 2.00| -  | Yes (2)      |
| 12      | M   | 39  | 21                     | 28               | 2.20| +  | Yes (2)      |
| 13      | M   | 30  | 36                     | 12               | 2.00| -  | No (0)       |
| 14      | M   | 38  | 22                     | 20               | 1.60| -  | No (0)       |
| 15      | M   | 38  | 20                     | 21               | 1.72| -  | Yes (1)      |
| 16      | M   | 52  | 14                     | 26               | 1.70| +  | Yes (5)      |
| 17      | M   | 49  | 13                     | 26               | 1.66| +  | Yes (2)      |
| 18      | F   | 40  | 13                     | 25               | 2.00| -  | Yes (2)      |
| 19      | M   | 51  | 23                     | 14               | 1.70| -  | No (0)       |
| 20      | F   | 44  | 16                     | 16               | 2.00| +  | Yes (2)      |
| 21      | M   | 28  | 14                     | 14               | 1.58| -  | No (0)       |

HLR, heart-to-lung ratio of antimyosin uptake (see text); BX, results of endomyocardial biopsy at the time of the antimyosin study; +, biopsy showing myocyte damage; −, normal biopsy or biopsy showing round cell infiltrate but not myocyte damage.

*Figures in parentheses indicate the number of rejection episodes detected in individual patients during follow-up.

of biopsies during the study divided by the number of months of follow-up and multiplied by 100 (percentage of positive biopsies per month during the study interval). Development of tolerance to the graft was analyzed on the basis of the percentage of reduction of rejection episodes between both intervals in individual patients according to the following formula: (P1−P2)/P1×100.

Results

Of the 21 patients, nine had absent antimyosin uptake, and in 12, abnormal antimyosin uptake was detected. Eighteen of the 102 biopsies (17.6%) performed revealed myocyte damage. At the end of follow-up, all patients were alive and one had suffered vascular rejection that was reversed with medical treatment.

At the time of antimyosin study, biopsy-antimyosin correlation revealed that the nine patients with absent antimyosin uptake also had a negative biopsy; in eight, a positive antimyosin scan coexisted with a negative biopsy, and four patients had rejection at biopsy and a positive antimyosin study. Detection of rejection in subsequent biopsies in these groups involved one (11%), four (50%), and four (100%) patients, respectively (Table 1).

Occurrence of Rejection in Subsequent Biopsies According to Presence and Degree of Antimyosin Uptake

The groups of patients with normal and abnormal uptake were comparable in relation to age, time elapsed from transplantation, months of follow-up, and number of biopsies performed (Table 2). Rejection, however, was detected in one of nine (11%) patients in the normal antimyosin group and in eight of 12 (67%) in the myocardial uptake group (p=0.03) (Table 1, Figure 1). Of the 18 rejection episodes detected, only one occurred in the patients in the normal antimyosin group, and the remaining 17 concentrated in the 12 patients with abnormal scans; the number of rejection episodes per patient was 0.11±0.33 and 1.41±1.44 (p<0.01). The total number of rejection episodes from transplantation to the end of follow-up was 1.4±1.5 and 5.2±2.7 (p<0.01), respectively. Left ventricular function at the end of follow-up as assessed by echocardiographic calculation of left ventricular fractional shortening was similar in both groups of patients.

To evaluate if the degree of antimyosin uptake was associated with a greater probability of biopsy-proven rejection during follow-up, patients were grouped according to those with a normal (nine patients), low (seven patients), and high (five patients) heart-to-
lung ratio. The groups of patients had similar ages, times elapsed from transplantation, months of follow-up, and numbers of biopsies performed. During follow-up, a trend was noted in which the percentage of patients who rejected, the mean number of rejection episodes per patient during the study, and the total number of rejection episodes since transplantation increased according to both the presence and degree of antimyosin uptake (Figure 2, Table 3). One patient in the group with high antimyosin uptake, with a heart-to-lung ratio greater than 2.00, developed vascular rejection that was successfully managed with medical treatment.

Development of Tolerance to Graft and Antimyosin Uptake

The mean number of rejection episodes detected by biopsy during the study in the 21 patients was 0.86±1.28 (range, 0–5). These same patients had suffered a mean of 2.52±1.89 (range, 0–8) rejection episodes during their first year after heart transplantation ($p<0.001$). The percentage of positive biopsies per month was also lower during the study period (P2) when compared with the first year after heart transplantation (P1), that is, 0.65±0.99 versus 1.62±1.21, respectively ($p<0.001$). These data are consistent with the well-known reduction in rejection activity after transplantation.

The percentage of reduction in rejection activity between both intervals, however, was different in the patients in the two antimyosin groups (Table 4). During the first year after transplantation, rejection activity had been significantly increased in the patients in the normal antimyosin group as compared with the patients in the normal group, or 3.4±1.7 versus 1.3±1.3 rejection episodes per patient ($p<0.01$) and 2.19±1.14% versus 0.85±0.85% rejection episodes per biopsy per month ($p<0.01$). The percentage of reduction of rejection episodes between the first year after heart transplantation and the study period was 57±40% in the patients in the abnormal antimyosin group and 95±10% in the patients in the normal antimyosin group ($p<0.03$). Thus, development of tolerance to the graft had been quicker in those patients who showed a normal antimyosin study than in those patients in whom myocardial uptake of antimyosin had been detected. When groups of patients were divided according to both the presence and degree of antimyosin uptake

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Scatterplot showing results of an antimyosin study performed in 21 patients after 1 year after heart transplantation, and occurrence of rejection detected at endomyocardial biopsy. A heart-to-lung ratio quantifies the presence and degree of antimyosin uptake. A cutoff point is set at 1.55 to differentiate normal vs. abnormal ratios.

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Scatterplot showing results of antimyosin studies performed in 21 patients after 1 year after heart transplantation, according to both the presence and degree monoclonal antimyosin antibody uptake related to the occurrence of biopsy-proven rejection. A heart-to-lung ratio quantifies the presence and degree of antimyosin uptake. A cutoff point is set at 1.55 to differentiate normal vs. abnormal ratio, and at 1.75 to assess the degree of antimyosin uptake (see text).
TABLE 3. Clinical and Biopsy Features of Patients With Heart Transplantation According to the Presence and Degree of Antimyosin Uptake

<table>
<thead>
<tr>
<th>Heart-to-lung ratio</th>
<th>Normal (n=9)</th>
<th>Low (n=7)</th>
<th>High (n=5)</th>
<th>p&lt;0.05*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>39±10</td>
<td>41±10</td>
<td>39±6</td>
<td>NS</td>
</tr>
<tr>
<td>Heart transplantation to antimyosin interval (mo)</td>
<td>24±10</td>
<td>19±7</td>
<td>24±10</td>
<td>NS</td>
</tr>
<tr>
<td>Antimyosin study to latest follow-up (mo)</td>
<td>16±5</td>
<td>20±5</td>
<td>19±7</td>
<td>NS</td>
</tr>
<tr>
<td>Number of biopsies per patients performed during the study</td>
<td>4.1±1.2</td>
<td>5.5±1.6</td>
<td>5.2±1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Patients who rejected during the study</td>
<td>1 (11%)</td>
<td>4 (57%)</td>
<td>4 (80%)</td>
<td></td>
</tr>
<tr>
<td>Number of rejection episodes during the study</td>
<td>1</td>
<td>9</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Rejection episodes/patients during the study</td>
<td>0.11±0.3</td>
<td>1.28±1.7</td>
<td>1.60±0.8</td>
<td>NL/HI</td>
</tr>
<tr>
<td>Total number of rejection episodes/patient since transplantation</td>
<td>1.4±1.6</td>
<td>4.2±2.7</td>
<td>6.2±2.5</td>
<td>NL/LO</td>
</tr>
<tr>
<td>Fractional shortening (echocardiography) (%)</td>
<td>34±6</td>
<td>31±8</td>
<td>33±5</td>
<td>NS</td>
</tr>
</tbody>
</table>

NL, patients with normal antimyosin uptake; LO, patients with low antimyosin uptake; HI, patients with high antimyosin uptake (see text); NS, not significant.

*One-way analysis of variance with multiple range test during Tukey-HSD procedure.

(Table 5), it was shown that tolerance to the graft was quicker in the patients in the normal group, but no differences were detected between the patients in the low and high antimyosin uptake groups.

Discussion

During the first few months after heart transplantation, patients invariably show myocardial uptake of monoclonal antimyosin antibody, revealing the presence of active myocardial damage. During the first year, a gradual decrease in myocardial uptake is observed that is paralleled by a progressive reduction in the number of rejection episodes at biopsy. After the first year, some patients show normal antimyosin studies, whereas in other patients, persistent myocardial uptake of antimyosin is detected. The present report reveals that at this time after transplantation, rejection was seldom detected during follow-up in patients with normal antimyosin studies, whereas rejection episodes were observed in 67% of those patients with abnormal scans. Furthermore, a trend was noted in which increasing degrees of antimyosin uptake correlated with a higher probability of detecting rejection at biopsy during follow-up. Antimyosin studies also reflected the total number of rejection episodes since transplantation.

The number of rejection episodes per patient detected at biopsy was greater during the first year after transplantation than during the study interval (which started an average of 22 months after the surgery). This is in agreement with the long-term reduction of rejection activity after transplantation (i.e., the so-called development of tolerance to the graft). This reduction took place in patients with both normal and abnormal antimyosin studies; however, the percentage of reduction of rejection episodes between the two intervals was significantly greater in the patients with normal antimyosin studies. Thus, development of tolerance to the graft was quicker in patients with a normal antimyosin study than in those who had myocardial antimyosin uptake.

These results indicate that tolerance varies from patient to patient, and that this is reflected on antimyosin studies performed after 1 year after heart transplantation.

Therefore, in monoclonal antimyosin studies performed after the first year after heart transplantation,
the presence and probably the degree of antimyosin uptake provide a noninvasive indicator of the rejection activity in individual patients.

**Significance of Positive Antimyosin Studies in Presence of Negative Endomyocardial Biopsies**

The discrepancy between the positivity of antimyosin studies in the absence of myocyte damage at endomyocardial biopsy has been described both in cardiac rejection after heart transplantation and in other types of diffuse myocardial damage, but its significance is not clearly understood. In patients with heart transplantation, Frist and colleagues found two patients with negative biopsies and positive scans; in a recent publication, we reported the results of 53 antimyosin studies in patients with heart transplantation, in whom 15 positive antimyosin scans coincided with negative biopsies. Yasuda and coworkers, in a series of 28 patients with acute myocarditis, found eight patients with a positive antimyosin study who did not show myocarditis at biopsy. In a recent paper, we have described such a discrepancy in 16 of 17 patients with chronic idiopathic stable dilated cardiomyopathy. The cause of such discrepancy remains unanswered. In this respect, heart transplantation provides a unique human model to adequately interpret such findings. In the present study, long-term follow-up of eight such patients revealed biopsy-proven rejection episodes in four. This fact probably indicates the presence of a sampling error of endomyocardial biopsy in the detection of rejection-induced cell damage after transplantation. This is not surprising because, in rejection as in myocarditis, the distribution of myocardial cell damage is patchy, which indicates that imaging with monoclonal antimyosin antibodies probably constitutes a more sensitive technique than interpretation of myocardial samples taken at endomyocardial biopsy in the detection of rejection-induced myocyte damage.

**Biopsy or Antimyosin Studies in Decision to Treat for Rejection?**

If a negative biopsy does not exclude the presence of rejection activity due to sampling error, should transplanted patients be treated for rejection according to antimyosin or to biopsy results? The body of knowledge regarding heart transplantation indicates that, in general, patients who show absent rejection in sequential biopsies do well, whereas those who have repeat rejection episodes do worse. In an earlier report, we suggested that antimyosin studies might be too sensitive to form the basis of the decision to treat or not to treat for rejection, and reliance on these data would probably lead to overimmunosuppression. If treatment for rejection is based on biopsy results, the use of monoclonal antimyosin studies after heart transplantation could be questioned.

**Role of Antimyosin Studies After First Year of Heart Transplantation in the Management of Patients**

Guidelines for long-term management of patients with transplantations are lacking. Should patients, after the first year after transplantation, be biopsied yearly or every 4 months? Should a similar degree of immunosuppressive treatment be given to all patients? Results reported herein indicate that with standard nonindividualized immunosuppression with cyclosporine and steroids, one group of patients attains an adequate level of suppression of rejection activity (i.e., normal antimyosin study), whereas in other patients who show persistent myocardial uptake, such a treatment might be inadequate. In the group of patients with an adequate level of suppression, and probably after the first year of transplantation, noninvasive follow-up could be considered. Unpublished observations in our laboratory while performing repeat studies in these patients indicate that a steady state of tolerance is kept during long-term follow-up (Figure 3). In such patients, biopsies can be avoided and surveillance of rejection with antimyosin studies can be done at longer intervals (Figure 4). This approach could be especially useful in children with heart transplantation.

Patients with myocardial uptake of antimyosin after the first year pose a different problem. The pertinent question is whether rejection activity, as detected by such technique, is clinically relevant and therefore should be treated or, on the contrary, whether such rejection activity is compatible with an uneventful clinical course and could be left untreated. Two basic arguments favor close surveillance...
of these patients. First, myocyte damage was detected at some stage during follow-up, in biopsies performed three times a year, in 67% of patients with abnormal antimyosin study and in 80% of those patients showing a heart-to-lung ratio greater than 1.75 (high-uptake group). It is probable that less frequent surveillance (i.e., every year) in this subgroup would have led to an undetected smoldering rejection activity and to undertreatment. In this respect, two earlier series of patients treated with cyclosporine in whom foci of myocyte damage were disregarded as unimportant were followed by an increased mortality.15,16 Second, there is evidence to indicate that rejection activity (the number of biopsy-proven rejection episodes) could influence the incidence of vascular rejection. Recently, Gao and coworkers17 have reported a higher incidence of rejection episodes in those patients who were retransplanted for coronary artery disease than in those who did not show coronary obstruction. In this series, the incidence of vascular rejection was as high as 44% a mean of 4.4 years after transplantation.17 The group of patients with high antimyosin uptake, who reflect a population at high risk for developing rejection could be also associated with a higher probability of occurrence of vascular rejection. In the present series, one patient with a very high antimyosin uptake after the first year after transplantation developed vascular rejection. Recent observations in our laboratory reveal that a heart-to-lung ratio greater than 2.00 after the first 3 months after transplantation was seen in 15 antimyosin studies; coinciding with such studies, vascular rejection was detected in three patients (20%), whereas no vascular rejection was detected at the time of 124 antimyosin studies in patients with heart-to-lung ratios of less than 2.00 (unpublished observations). Therefore, untreated rejection activity in patients with a very high uptake of antimyosin detected after the first year after transplantation could lead to the eventual formation of coronary lesions and its progression to severe obstructive vascular disease. Frequent biopsies and perfusion studies with TI-201 would be appropriate in these high-risk patients (Figure 4), and treatment for interstitial and vascular rejection should be instituted when detected.

In the present study, the effects of the excess rejection episodes on left ventricular function in the patients in the group with persistent antimyosin uptake were not apparent, as left ventricular contrac-
tion was similar in patients with normal or abnormal antimyosin uptake. This contrasts with results recently reported by the Stanford group,18 who have provided evidence of the deleterious effect of cumulative rejection episodes on myocardial function. A limitation of the present study is the assessment of left ventricular function by a relatively late indicator of myocardial dysfunction, the fractional shortening of the left ventricle. It is likely that by using finer analyses of ventricular function, groups of patients at risk for developing left ventricular dysfunction would parallel those described herein, according to the presence and degree of antimyosin uptake.

Acknowledgments
We express our gratitude to Gaietà Permanyer, MD, for careful review of the manuscript, and to Carme Casanovas for her excellent secretarial work.

References

KEY WORDS • heart transplantation • rejection • monoclonal antibodies • nuclear medicine • antimyosin
Indium-111-monoconal antimyosin antibody studies after the first year of heart transplantation. Identification of risk groups for developing rejection during long-term follow-up and clinical implications.

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Circulation. 1990;82:2100-2107
doi: 10.1161/01.CIR.82.6.2100

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