Acute Rejection in the Long-Term Cardiac Transplant Survivor

Clinical Diagnosis, Treatment and Significance

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SUMMARY
Thirty-two of 59 patients undergoing cardiac transplantation at Stanford University Medical Center since January, 1968, have survived longer than three months. In 19 of these long-term survivors 47 episodes of late acute rejection occurred. In the first two months post-transplantation the incidence of acute rejection is one episode per 20.5 patient days, but between four and 12 months post-transplantation decreases to one episode per 200 patient days. Late acute rejection episodes are usually clinically mild and can be detected by electrocardiographic changes, evidence of mild graft dysfunction and characteristic histologic changes in tissue obtained by transvenous endomyocardial biopsy. Out-patient treatment with increased oral prednisone has successfully reversed 70% of these late acute rejection episodes, with the other 30% requiring more aggressive therapy. Late acute rejection or complications related to its treatment have contributed to the death of three long-term survivors and has been implicated as a causative factor in the development of graft coronary atherosclerosis in six patients in the earlier part of our series. However, the occurrence of acute rejection in the long-term cardiac transplant patient does not preclude good graft function and patient survival in the majority of patients.

Additional Indexing Words:
Cardiac transplantation  Cardiac rejection  Immunosuppression  Endomyocardial biopsy

Acute graft rejection and the consequences of its treatment continue to be the major factors limiting survival of the patient with a cardiac allograft. The recognition and treatment of acute rejection in the early postoperative period has been previously described in detail. In contrast, little information has been presented on the incidence and significance of late acute graft rejection in the long-term cardiac transplant survivor. Thirty-two patients in the Stanford cardiac transplantation series have lived more than three months after operation. Our experience with the diagnosis and treatment of acute rejection episodes in these long-term survivors form the basis for this report.

Patients and Methods
Fifty-nine patients have undergone cardiac transplantation for end-stage cardiac disease at the Stanford University Medical Center between January, 1968, and June, 1973. Our experience with patient selection, tissue typing, operative technique and early postoperative care has been detailed in previous publications. At this time actuarial survival for the entire series is 43% at one year, 40% at two years and a projected 26% at three years. In those patients undergoing transplantation since 1970, there has been an over-all 50% one year survival rate. Thirty-two patients (54.4%) in this series survived longer than three months after transplantation, for a current total survival of 50.8 patient years. There are at this time 23 surviving recipients, of whom 20 lived for periods of three to 49 months following operation.

Immunosuppression
Cardiac transplant patients are maintained indefinitely on long-term immunosuppressive therapy (table 1). At three months post-transplantation the usual daily prednisone dose is 0.75 mg/kg, which is reduced at six
Table 1

Immunosuppression in Long-term Cardiac Transplant Patients at Stanford

<table>
<thead>
<tr>
<th>Daily maintenance</th>
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<tbody>
<tr>
<td>*Prednisone 0.25–0.75 mg/kg</td>
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<tr>
<td>Azathioprine 2–3 mg/kg</td>
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<tr>
<td>or</td>
<td></td>
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<tr>
<td>Cyclophosphamide 1–1.5 mg/kg</td>
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<tr>
<td>Initial therapy for acute rejection</td>
<td></td>
</tr>
<tr>
<td>Prednisone 1 mg/kg/day</td>
<td></td>
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<tr>
<td>Reduced over two weeks to maintenance level</td>
<td></td>
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<tr>
<td>Recurrent or severe acute rejection</td>
<td></td>
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<tr>
<td>Methyl-prednisolone 1000 mg/day × 3 days (I.V.)</td>
<td></td>
</tr>
<tr>
<td>Antithymocyte globulin 4000 rosette inhibition units/kg/day × 3–5 days (I.V.)</td>
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*In selected patients alternate day dose is employed.

months to a daily dose of 0.25–0.5 mg/kg. A recent trial of every-other-day prednisone therapy has been initiated in several stable long-term survivors. The usual daily prednisone dose is doubled and given on alternate days. The preliminary results of this trial indicated that it is possible to maintain certain long-term survivors on this regimen. Prior to September, 1972, all patients received azathioprine 2–3 mg/kg/day. Since that time some new patients have received cyclophosphamide 1–1.5 mg/kg/day instead of azathioprine.

Long-Term Follow-Up

After discharge from the hospital clinical examination is performed once or twice a week for the first year and twice a month thereafter. Upon each visit a standard electrocardiogram, chest roentgenogram, complete blood count and differential, prothrombin and proconversion time and chemistry screening battery are performed. The same Elema–Scholander electrocardiogram machine is used to record all electrocardiograms, and uniform placement of the precordial leads is assured by tattooing of the chest. The total QRS voltage is measured in leads I, II, III, V₁ and V₆ and summed to give sigma (Σ) value, which is used as a measure of the electrical activity of the heart. The electrocardiogram is also reviewed for the occurrence of arrhythmias and conduction abnormalities.

Diagnosis of Acute Rejection

Clinical Grading

The clinical diagnosis of acute rejection in a patient with a cardiac allograft is based on evidence of graft dysfunction. The same criteria are used in the diagnosis of late acute rejection as previously established for acute rejection which occurs in the early post-transplant period. Late acute rejection episodes have been clinically categorized as follows: 1) Mild—no symptoms of congestive heart failure or diminished cardiac output at rest or following moderate exertion. Electrocardiographic findings of a decrease in the (Σ) voltage QRS and/or arrhythmias frequently constitute the only indications of rejection. A soft diastolic gallop sound may be present. 2) Moderate—no clinical evidence of impaired myocardial performance at rest, but reduced exercise tolerance is noted. 3) Severe—clinical evidence of impaired myocardial performance at rest with symptoms of weakness and evidence of reduced cardiac output and congestive heart failure.

Transvenous Endomyocardial Biopsy

Serial right ventricular endomyocardial biopsies of the human heart have allowed direct histologic examination of the myocardium during clinically suspected rejection episodes. The technique and biotome are modifications of the methods used by Konno-Sakakibara. This procedure is performed serially on each new cardiac transplant patient in the early postoperative period and has become an important diagnostic tool for the care of these patients. Endomyocardial biopsy is also performed on each stable long-term survivor in order to obtain a baseline for future reference, and repeated when acute rejection is clinically suspected. Since July, 1972, there have been no significant complications as a result of 73 biopsies in 23 transplant patients.

Treatment of Late Acute Rejection

Mild acute rejection in the long-term cardiac transplant patient is treated on an out-patient basis (table 1). The current maintenance dose of oral prednisone is doubled for two days and then tapered back to the previous maintenance dose over approximately 10–14 days. During this period frequent electrocardiograms and patient examinations are used to evaluate the effectiveness of therapy and to detect possible complications of treatment. Repeat endomyocardial biopsy is performed ten days following initiation of treatment to confirm the complete reversal of the histologic signs of rejection. Patients not responding satisfactorily to this regimen, indicated by continuing signs of rejection on biopsy or who have frequent recurrence of clinical rejection, are hospitalized. Treatment for these episodes of late acute rejection then consists of daily high-dose intravenous methyl-prednisolone and equine antihuman thymocyte gamma globulin* for three to five days (table 1). The treatment of the severe, late acute rejection episode is similar to that in all rejection episodes occurring in the first two months following surgery.

Results

Incidence of Late Acute Rejection

There have been 47 diagnosed episodes of acute rejection occurring later than three months after operation in 19 of 32 long-term transplant survivors. Seven of these patients had only one episode each, while three patients had five episodes of late acute rejection. In the period from four to 12 months following operation this represented one episode of

*Supplied by Upjohn and Company, Kalamazoo, Michigan.
Acute rejection per 200 patient days of follow-up, which further decreased to one episode per 325 patient days in the period from 13 to 24 months post-transplantation (fig. 1). This is in contrast to one episode of acute rejection per 20.5 patient days in the first two months following transplantation.

**Diagnostic Features of Late Acute Rejection**

Seventy-two percent of late acute rejection episodes were not associated with clinical symptoms of cardiac dysfunction at rest or during exercise (table 2). Changes in the electrocardiogram were seen in all episodes of late acute rejection (table 2). There was an average 32% decrease in the total (Σ) QRS voltage during 96% of diagnosed rejection episodes. Fifty-two percent of the episodes were associated with transient arrhythmias which included atrial premature contractions (28%), ventricular premature contractions (15%), atrial flutter (17%) and atrial fibrillation (2%). Conduction abnormalities were present in 23%.

The most frequent clinical findings consisted of diastolic filling sounds which were heard in 47% of rejection episodes. Peripheral edema was noted in 17% of the episodes, but other signs of more serious graft dysfunction were unusual.

**Transvenous Endomyocardial Biopsy Results**

Since July 1972, serial biopsies have been performed during six episodes of acute rejection in four long-term survivors. The histologic changes of late acute rejection were similar to those seen during acute rejection occurring in the first two month period following operation. Biopsies prior to treatment consistently showed inflammatory cell infiltration, endocardial thickening, interstitial edema and variable amounts of myocytolysis (fig. 2). In addition, there has been a variable amount of endomyocardial fibrosis in certain patients. Some lymphocytes staining positively with Methyl-Green-Pyronin indicating immunological activity, were frequently seen. In four out of six episodes of late acute rejection (fig. 2) repeat biopsy following treatment has shown a marked reduction in the inflammatory cell infiltrate as well as interstitial edema and endocardial thickening. Histologic improvement correlated well with resolution of the clinical manifestations of acute rejection in those patients responding to treatment. In the other two remaining episodes, which failed to respond to treatment, serial biopsies showed only slight improvement in the cellular infiltrate in addition to severe myocyte damage and fibrosis.

**Response To Treatment**

Thirty-four mild episodes (72%) of late acute rejection in 17 patients have been treated initially.
on an out-patient basis (table 3). The average increase in oral prednisone was 194% over maintenance levels, and this was tapered back to the previous maintenance doses over an average period of 15 days. Resolution of electrocardiographic changes and other signs of graft dysfunction occurred in 31 of the 34 episodes following treatment.

Hospitalization was required for more aggressive treatment of three clinically mild episodes in two patients failing to respond to increased oral steroids, and 13 clinically more severe episodes in three other patients (table 2). Each of these episodes was treated with intravenous methylprednisolone in an average dose of 2.2 gm given over an average of 2.6 days. Antithymocyte globulin in a dose of 4000 rosette inhibition units per kilogram per day was given intravenously for three days in 15 of these episodes. In addition, actinomycin 250 μg was given intravenously as a single dose in three episodes of severe late acute rejection. This treatment schedule successfully reversed all clinical and histologic signs of rejection in ten of these 16 episodes. Residual findings of late acute rejection and graft dysfunction following treatment were seen in six episodes occurring in three patients.

Complications of Late Acute Rejection

The relationship between the occurrence of acute rejection in long-term survivors, its treatment and subsequent complications, has been determined. Three deaths have occurred among the 32 long-term survivors as a direct result of acute rejection or its treatment. In each case the patient had repeated episodes of moderate or severe late acute rejection which did not fully respond to intensive treatment.

Table 3

<table>
<thead>
<tr>
<th>Rejection grade (no. of episodes)</th>
<th>In-patient therapy</th>
<th>Out-patient therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Moderate</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>In-patient therapy</th>
<th>Out-patient therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average increase of prednisone (%)</td>
<td>194</td>
<td>194</td>
</tr>
<tr>
<td>Duration of therapy (days)</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Methyl-prednisolone</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Anti-thymocyte globulin*</td>
<td>4000</td>
<td></td>
</tr>
<tr>
<td>Duration of therapy (days)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Actinomycin D (μg)</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td>Duration of therapy (days)</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response to treatment</th>
<th>In-patient therapy</th>
<th>Out-patient therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete reversal</td>
<td>10</td>
<td>31</td>
</tr>
<tr>
<td>Residual rejection or recurrence</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Death due to rejection</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Death related to rejection therapy</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

*Supplied by Upjohn & Co., Kalamazoo, Michigan.
Continuing severe graft dysfunction was present following treatment in each case. Two of these patients subsequently died of overwhelming sepsis occurring during treatment of late acute rejection. In each patient endomyocardial biopsy and subsequent autopsy examination of the heart confirmed the presence of extensive fibrosis and severe myocyte damage, in spite of the presence of only minimal inflammatory infiltrate.

Six long-term survivors in the early part of our series died between eight and 45 months following transplantation as a direct result of the complications of graft coronary artery atherosclerosis. In each case, the findings at autopsy were those of variable degrees of intimal hyperplasia, lipid infiltration and fibrosis in all major coronary arteries. Twenty-two of the current long-term survivors did not show signs of significant coronary atherosclerosis for periods up to 49 months following surgery, as judged by exercise electrocardiography and yearly coronary arteriography. The average incidence of acute rejection during the total post-transplant course of those patients developing coronary atherosclerosis was 2.8 rejection episodes per patient, as compared with 1.3 rejection episodes per patient in more recent patients not developing these changes. In addition, the patients developing graft coronary artery atherosclerosis had an average of one severe rejection episode per patient, as compared with 0.3 severe rejection episodes per patient in the current group not having these changes. Analysis of other possible factors relating to the occurrence of these changes is presently under way.

Discussion

Our experience in the care of the long-term cardiac transplant survivor now encompasses 50.8 patient years. It is evident that acute graft rejection episodes during the late post-transplantation period occur at a much reduced frequency when compared to those during the first few months following operation, but may occur even three years after transplantation (fig. 1). Since most episodes do not result in clinical symptoms of graft dysfunction, it is possible that the true incidence of late acute rejection is higher than reported. In spite of the fact that most rejection episodes are clinically mild and respond to treatment, approximately 10% of patients develop severe late acute rejection leading to irreversible graft dysfunction and death. Whether the occurrence of these severe episodes could be completely prevented is unclear, but it is likely that earlier treatment may prevent residual myocardial damage. Therefore, it is essential to continue to monitor patients indefinitely for early signs of acute rejection throughout the long-term follow-up period. This aggressive approach to early diagnosis and treatment may have prevented damage to the myocardium in 16 of the 19 patients suffering late acute rejection episodes in this series, as documented by long-term hemodynamic studies.

Endomyocardial biopsy has proved to be a useful technique for identification of the histologic changes associated with acute rejection. There has been good correlation between the clinical assessment of allograft function during rejection and the histologic changes seen on endomyocardial biopsy. Biopsies obtained on patients who are clinically stable revealed normal-appearing myocardium. The severity of the rejection process can be accurately graded from the biopsy and modifications in the immunosuppressive therapy. It is hoped that repeat biopsy after treatment, to confirm the complete reversal of the histologic changes, will assure appropriate treatment and therefore prevent permanent damage to myocytes and resultant fibrosis. In those patients with a poor clinical response to treatment of rejection, a repeat endomyocardial biopsy is used to differentiate continued rejection from residual myocyte damage.

Treatment of acute rejection in the long-term survivor is usually successful, particularly if the findings of graft dysfunction are mild (table 3). Most patients continue near normal activities during treatment of the rejection episode. Treatment of these mild episodes has not been associated with any direct morbidity. The occurrence of repeated episodes of late acute rejection increases the risk of permanent graft dysfunction or death due to the complications of treatment. This experience is similar to the early period following surgery when the frequent occurrence of acute rejection markedly decreases the risk of long-term survival.

The precise mechanisms responsible for the continued occurrence of acute rejection in the long-term survivor remain unclear. Four episodes of late acute rejection occurred within two weeks after tapering of maintenance prednisone, suggesting inadequate immunosuppression as a factor in these instances. Immunologic mechanisms are still operative in the late acute rejection episode, as lymphocytes and plasma cells staining with Methyl-Green-Pyronin are frequently present in biopsy.
specimens. These cells may play a role in producing myocyte and vascular damage.

The relationship between the occurrence of acute rejection in the long-term survivor and the development of graft coronary artery atherosclerosis in the transplanted heart merits discussion. Damage to the coronary arterial intima has been histologically documented during acute rejection episodes and may be a factor predisposing to the future development of graft atherosclerosis. The frequency and severity of acute rejection may be a factor in the development of these changes, but further analyses of all possible risk factors is necessary before a final conclusion can be drawn. It should be stressed that there has been an apparently marked decrease in the appearance of these changes in the more recent long-term survivors in this series.

The fact that acute rejection occurs less frequently, and is less severe clinically and histologically, suggests that a state of limited tolerance does develop in the majority of long-term survivors. This is similar to the experience with renal allografts and supports our hypothesis that long-term survival of the cardiac allograft can be expected in those patients surviving the critical first few months after operation.

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