The Status of Cardiac Transplantation, 1975

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SUMMARY
Since December 1967, 263 human cardiac transplant operations have been performed throughout the world. Eighty-two of these were performed at Stanford University Medical Center. In 1974, 27 such operations were performed, 15 at Stanford. Survival rates for the entire Stanford series are 48% at one year and 25% at three years; survival rates at one and three years for patients surviving the first three critical months after transplantation are 77% and 42%, respectively. Recipients under the age of 55 years, with New York Heart Association Class IV cardiac disability, are selected for transplant procedures according to criteria dictated by experience over the past seven years.
A routine immunosuppressive regimen for organ transplantation, incorporating prednisone, azathioprine, and antithymocyte globulin is employed early postoperatively, and prednisone and azathioprine are used for indefinite maintenance therapy. Acute cardiac graft rejection in nearly all recipients is diagnosed by clinical signs, electrocardiographic changes, and percutaneous transvenous endomyocardial biopsy. Ninety-five percent of acute rejection episodes are reversible with appropriate immunosuppressive treatment, but infectious complications are common and have accounted for 56% of all postoperative deaths.
The Stanford experience in cardiac transplantation has demonstrated the potential therapeutic value of this procedure. Maximum survival now extends beyond five years. Satisfactory graft function has been documented in long-term surviving patients, the majority of whom have enjoyed a high degree of social and physical rehabilitation.

MORE THAN SEVEN YEARS have elapsed since the first human cardiac allograft was transplanted by Barnard in December 1967. Since that time, 263 cardiac transplant operations have been performed by 64 teams in 22 countries. Following the initial enthusiasm with which cardiac transplantation was received, activity in this field declined rapidly as investigators became increasingly aware of the complex challenges involved. As a result, during 1974 only 27 heart transplants were performed worldwide; 15 of these procedures were performed at Stanford University Medical Center. Because of the predominant activity of Stanford in the field of cardiac transplantation at the present time, this review will be largely confined to experience developed at this Center.
The prolonged survival and rehabilitation of a significant percentage of patients after cardiac transplantation provide evidence for the therapeutic potential of the procedure as an alternative in the treatment of advanced heart disease. In this review, the major areas in cardiac transplantation will be summarized, with primary emphasis given to clinical aspects such as candidate selection and medical management of recipients during both early and late postoperative periods.

Survival Statistics
As of March 1, 1975, 82 patients have undergone cardiac transplantation at Stanford Medical Center since January 1968. Twenty-eight of these patients are still alive 1–62 months after transplantation.
Patient survival rates for the entire series, calculated by the actuarial method, predicts over-all
48%, 37%, and 25% survival at one, two, and three years, respectively. For those patients who survive the critical first three postoperative months, the one, two, and three year figures are 77%, 60%, and 42%, respectively.

In table 1, patient survival is summarized according to age at the time of transplantation. These data illustrate that younger patients have better survival rates. As a result, only patients under the age of 55 years are considered as candidates for cardiac transplantation at the present time. Reasons for the survival advantage of younger recipients are unknown but are consistent with previous observations in renal transplantation.²

Recipient Selection

Cardiac replacement provides an ultimate option in the treatment of patients with far-advanced, irreparable heart disease. To date, 114 patients have been selected as potential cardiac recipients. Data concerning diagnosis, age, and sex appear in table 2. These patients, however, represent only a small part of the total number of patients referred as potential candidates. In 1973, an average of 7.5 patient referrals for possible cardiac transplantation were received each month. Thirty percent of these were seriously considered for transplantation by evaluation at Stanford Medical Center, and a total of 18 patients were finally accepted formally as recipients during the entire year.

Our criteria for recipient selection dictate that the patient have New York Heart Association Class IV disability, secondary to symptoms of congestive heart failure, reduced cardiac output, or rarely, intractable angina pectoris, and that expectations for continued survival be limited to several months. The evaluation process includes a standard medical history, physical examination, and laboratory evaluation of renal, hepatic, gastrointestinal, neurological, pulmonary, hematological, and immunological status. Detailed cardiovascular investigations consist of electrocardiography, echocardiography, right and left heart hemodynamic measurements, left ventricular angiography, and in most cases, coronary arteriography. Advanced renal or hepatic dysfunction or significant gastrointestinal disease such as active peptic ulcer disease or diverticulosis constitute contraindications to operation. Any systemic infection or pulmonary infarction likewise prohibit selection. Finally, severe elevation of pulmonary vascular resistance secondary to long-standing left ventricular failure or pulmonary emboli, as manifested by a calculated pulmonary vascular resistance greater than 8 Wood units, precludes cardiac transplantation. In addition, a complete psychological evaluation is performed by our psychiatric social worker. A candidate must be emotionally stable and must not have any psychiatric disorder that would seriously limit functional rehabilitation postoperatively.

If there are no apparent contraindications, a frank discussion is then held with the patient and family. The following items are discussed in detail: 1) the prognosis without transplantation; 2) the immediate postoperative risk; 3) the long-term prognosis based on our own experience; and 4) the requirements for long-term postoperative follow-up and investigation after transplantation.

After informed consent is received, cardiac transplantation is performed as soon as a suitable donor becomes available. The interval between selection and transplantation has averaged 33 days, with a range of 1–208 days. In those cases in which the waiting recipient died before a suitable donor became available, the interval between selection and death has averaged 36 days, with a range of 1–262 days. The three-month survival of 32 patients selected, but not operated, is 16%, and the nine-month survival is 6%.

Donor Selection

Prior to the advent of clinical cardiac transplantation, it was assumed by most investigators that removal of a beating heart from a patient who had sustained irreversible brain death would result in

<table>
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<tr>
<th>Table 1</th>
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<tbody>
<tr>
<td>Postoperative Survival According to Age</td>
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<tr>
<td>Age (yrs) at transplant</td>
</tr>
<tr>
<td>11-20</td>
</tr>
<tr>
<td>11-20</td>
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<td>21-30</td>
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<td>31-40</td>
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<td>41-50</td>
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<td>51-60</td>
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<tr>
<td>61-70</td>
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<tr>
<td>Total</td>
</tr>
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( ) = Number of patients operated long enough ago that could have reached one or more years' survival.

Note: The discrepancy between the one- and two-year survival at age 31-40 is due to the fact that five of eight patients survived one year and the same five survived to two years. However, one patient has lived past one year, but has not yet reached two years' survival.

<table>
<thead>
<tr>
<th>Table 2</th>
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<tbody>
<tr>
<td>Recipients Selected for Transplantation</td>
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<tr>
<td>Preoperative diagnosis</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
</tr>
<tr>
<td>Radiation heart disease</td>
</tr>
<tr>
<td>Total</td>
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</table>
widespread public disapproval. To the contrary, in our experience, the general public has readily accepted the definition of brain death and the practical exigencies of organ donation. Indeed, in a majority of cases, it has been a family member of the prospective cardiac donor who has initiated action resulting in referral of the potential donor to our hospital. All cardiac donors in our series have been patients who have sustained catastrophic neurological injury resulting in irreversible brain death. In the majority of cases, the etiology has been nonpenetrating cranial trauma resulting from automobile accidents (table 3).

After admission to the neurosurgical service, the potential donor is evaluated by a committee of three independent neurosurgeons or neurologists. The diagnosis of irreversible brain death is based upon historical information, neurological examination, the results of electroencephalography, and in some cases, cerebral arteriography or operative findings at craniotomy. After the neurologists and neurosurgeons determine that there is no evidence of central nervous system function and no hope of return of function, members of the cardiac transplantation team assume management of the donor until cardiac arrest is performed. Careful assessment of cardiac function is performed on all donors. This includes left ventricular angiography and coronary arteriograms in donors over 35 years of age, and in those with suspected cardiac abnormalities. Three potential donors in our series have been excluded on the basis of such studies (traumatic mitral regurgitation in one, significant coronary artery disease in two).

Intensive care and vigorous supportive management are necessary for the maintenance of a satisfactory cardiovascular status in all donors. This is due largely to the multiple effects of brain death on cardiovascular control mechanisms. Mechanical ventilation, utilizing high concentrations of oxygen, is provided by an endotracheal tube. Control of body temperature within a physiological range is necessary, as most donors have exhibited hypothermia. Diabetes insipidus is often present as a result of pituitary destruction and requires frequent injections of vasopressin. Intravenous insulin is often required to control hyperglycemia and glycosuria. These latter factors contribute to diuresis, and careful attention must be directed to maintenance of satisfactory fluid and electrolyte balance. Sufficient fluid is administered to maintain central venous pressure in the range of 10–15 cm of water. The use of large doses of vasopressors is often not necessary after appropriate hydration, and the need to use these agents may indicate myocardial dysfunction.

Preoperative cultures of blood, respiratory tract secretions, and urine have been obtained in all cardiac donors. Many potential donors present evidence of established pulmonary infection at the time of referral, and all are treated with a high dose, broad spectrum antibiotic regimen prior to organ removal. In no case in our series has a postoperative infection in the cardiac recipient been traced to an organism detected in the cardiac donor.

### Tissue Typing

The desperate clinical status of patients awaiting cardiac transplantation precludes an excessive waiting period for a histocompatible donor. In all of our cases, ABO blood group compatibility and a negative crossmatch between recipient serum and donor lymphocytes are assured prior to transplantation. Retrospective analysis of our own histocompatibility data has failed to show a significant correlation between the numbers of HLA antigens mismatched and postoperative survival or rejection history. Presently we are reanalyzing our entire HLA typing data by weighing each donor-recipient antigen mismatch. This method is a modification of that described by Mickey et al., which has as its basis the probability of antibody response of HLA-typed multiparous women to the HLA antigens of the father. Very preliminary results of this analysis indicate that in a significantly high proportion of cases it may be possible on the basis of such a system of histocompatibility matching to discriminate between the extremes of post-transplant outcome (that is, those recipients likely to do well postoperatively and those likely to sustain severe, intractable graft rejection). This methodology, however, does not take into account additional factors that may influence the host immune response, such as unidentified HLA loci, mixed lymphocyte culture loci, and over-all immune responsiveness. The impact of these additional variables on transplantation between unrelated donors is yet to be defined.

### Operative Techniques

Operative techniques currently employed for human cardiac transplantation are similar to those...
originally described for the canine model, with some modifications dictated by clinical experience. Venous cannulation for cardiopulmonary bypass is accomplished through the superior portion of the right atrium for both superior and inferior vena cavae. Arterial return is provided through the recipient ascending aorta. During the past five years there have been no postoperative complications directly attributable to this technique of cannulation.

Performance of the venous anastomoses at the midatrial level remains an essential feature of graft implantation. The donor right atrium is prepared for anastomosis by a curvilinear incision, beginning in the orifice of the inferior vena cava and extending upward and medially into the base of the right atrial appendage (a modification in technique originally suggested by Barnard). The stump of the donor superior vena cava is ligated. By virtue of this maneuver, the donor sinoatrial node is protected from the trauma of a continuous suture line. Despite meticulous attention to the level of atrial resection and positioning of suture lines, however, transient abnormalities in donor atrial rhythm are commonly encountered during the first several postoperative days.

Myocardial viability in the donor heart is maintained during the period of transfer into the recipient by simple hypothermic preservation. This is achieved by immersion of the graft in cold saline at 4°C Centigrade. Graft ischemia times in our series have ranged from 30–82 minutes (average 48 minutes). Such intervals are well within safe limits previously established for satisfactory myocardial preservation by simple hypothermia.

Because of the frequent occurrence of donor heart bradycardia during the early postoperative period, temporary pacemaker wires are attached to the graft. Donor atrial pacing, when required, has been readily achieved with atrial epicardial wires (bipolar mode) and is superior functionally to ventricular pacing. In addition, daily atrial electromyograms recorded directly from the donor atrial wires have been helpful in the diagnosis of acute rejection episodes (see below). In most cases, a dilute intravenous infusion of isoproterenol is given for the first 2–4 postoperative days, beginning at the discontinuation of cardiopulmonary bypass. As discussed later, the positive myocardial inotropic and chronotropic effects of isoproterenol significantly enhance graft function during the early postoperative period.

Early Postoperative Management

Immunosuppression

In general, our methods for immunosuppression following cardiac transplantation are similar to those employed for renal transplantation. Prednisone and azathioprine or cyclophosphamide constitute the primary immunosuppressive agents, combined with antithymocyte globulin during the early postoperative period and during subsequent severe rejection episodes. A loading dose of azathioprine orally (4 mg/kg) or cyclophosphamide intravenously (5 mg/kg) is given immediately prior to operation. Beginning on the first postoperative day, maintenance treatment with azathioprine at a dose of 2–3 mg/kg/day or cyclophosphamide at a dose of 1–1.5 mg/kg/day is begun and continued in the highest tolerated dose, as determined by measurement of peripheral white blood cell and platelet counts. Wide variations in drug tolerance have been encountered, and in some patients long-term maintenance doses have been considerably lower than those noted above. Methylprednisolone is given intravenously in a dose of 10 mg/kg shortly after discontinuation of cardiopulmonary bypass, and is continued on a six-hourly basis at a dose of 7.5 mg/kg/day on the first postoperative day, and 5 mg/kg/day on the second postoperative day. Maintenance oral prednisone is initiated on the first postoperative day in a dose of 2 mg/kg/day, and is gradually decreased over the first two postoperative weeks to a maintenance dose of 1 mg/kg/day.

Antihuman thymocyte globulin of either horse or rabbit origin has been used in various regimens. In early patients, the equine preparation was generally administered intravenously with gradually diminishing frequency over the first six postoperative weeks. Currently, rabbit antithymocyte globulin (RATG) is administered intramuscularly. Dosage is based upon the spontaneous rosette inhibition test. The concentration in μg/ml which will inhibit by 25% the number of rosettes formed in a human lymphocyte-sheep erythrocyte mixture is the rosette inhibitory "titer" (RIT). The standard dose has been 4 mg/kg RATG with a 1 μg/ml RIT given intramuscularly on each of postoperative days 0, 1, 2, 4, 6, and 8. Although it is unlikely that the RIT is a measure of an ATGs immunosuppressive potency, recent measurements of circulating levels of serum rabbit globulin (RG) in patients posttransplantation indicate a correlation of 0.87 between peak level of serum rabbit globulin corrected for RIT and the interval between operation and onset of the first rejection episode. This data supports the concept that for any ATG prepared in a constant fashion, the RIT is at least proportional to immunosuppressive potency. RG half-life after discontinuation of RATG varies from 36 hours to 18 days. In patients with short half-lives a concurrent rise in levels of antirabbit globulin antibody can usually be detected, but only by radioimmunoassay.

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Early Postoperative Physiology

Heart rate, stroke index, and cardiac index have been measured during the first week after transplantation in ten patients. Stroke index and cardiac index were initially depressed at 21.4 ml/beat/m² and 1.83 L/min/m², respectively. Cardiac index subsequently rose in each patient to normal, or nearly normal levels by the third or fourth postoperative day. This early postoperative increase in cardiac index was due entirely to augmentation of stroke index, unassociated with significant changes in heart rate. Mean pulmonary artery pressure, which preoperatively averaged 36.1 mm Hg, was 26.4 mm Hg immediately after transplantation, and gradually decreased to 22.2 mm Hg over the first postoperative week.

The effects of isoproterenol on graft hemodynamics were studied in five of these patients within 24 hours of transplantation. Doses of isoproterenol ranged from 0.9 to 5.2 µg/min, and averaged 2.2 µg/min. Average increases in heart rate, stroke index, and cardiac index in response to isoproterenol were 46%, 123%, and 219%, respectively, as compared to the control state. For this reason, isoproterenol is now used routinely during the first two to four days after transplantation to enhance graft hemodynamic performance.

In addition, donor heart pacing via temporary pacing wires sutured to the donor right atrium at the time of operation is often required in the early postoperative period because of the development of low atrial or junctional rhythm at a suboptimal rate. In nearly all cases, however, this tendency toward graft bradycardia is transitory, and regular sinus rhythm at a satisfactory rate is established by the end of the first postoperative week.

Diagnosis of Acute Rejection

The clinical diagnosis of acute rejection in cardiac recipients is based on clinical evidence of graft dysfunction and histologic examination of the endomyocardium. A standard electrocardiogram is obtained twice daily during the early postoperative period, and the sites of recording for leads V₁ and V₆ are tattooed to eliminate positional variation. In addition, direct electromyograms are recorded with the exploring V lead from the atrial pacemaker wires. The algebraic sums of QRS voltages in leads I, II, III, V₁, and V₆ are measured. A decrease in this summated voltage, or in QRS voltage recorded through the atrial wire, greater than 20% of baseline is highly suggestive of acute cardiac allograft rejection. In addition, atrial arrhythmias, either atrial premature contractions or atrial flutter or fibrillation, suggest an acute rejection process.

The development of a third or fourth heart sound, as determined by physical examination or phonocardiography, also suggests acute graft rejection. These sounds are thought to be caused primarily by changes in ventricular compliance of the transplanted heart secondary to immune injury.

A technique for percutaneous transvenous endomyocardial biopsy through the right internal jugular vein has been developed at our center and has proved to be a valuable aid in the diagnosis and management of acute rejection episodes. Endomyocardial biopsies are usually obtained weekly in the early postoperative period, and in addition, upon the appearance of clinical signs suggesting impending acute rejection. This technique is also used routinely in the assessment of resolution of acute rejection after a course of augmented immunosuppression.

In a series of 67 patients, the first acute rejection episode was diagnosed an average of 12 days postoperatively. The average number of acute rejection episodes during the first 60 days after transplantation has been two episodes per patient, or one episode per 22 patient days.

Treatment of Acute Rejection

The initial treatment of a diagnosed acute rejection episode usually consists of intravenous administration of methylprednisolone, 1000 mg, for three consecutive days. Antithymocyte globulin, if it has previously been discontinued, is added during this same period. Oral doses of prednisone are increased to approximately 1.5 mg/kg/day and then gradually tapered to maintenance doses of 1 mg/kg/day over the subsequent 1–2 weeks. Actinomycin D, in doses of 200 µg daily, intravenously, is often given for two to three days during the first rejection episode. In addition, heparin given intravenously in doses sufficient to prolong the whole blood thromboplastin time to 2.0–2.5 times normal levels is administered for five to seven days. Anticoagulation with heparin is provided in an attempt to prevent platelet and fibrin deposition in small coronary vessels damaged by the rejection process. Serial endomyocardial biopsy has aided greatly in the manipulation of immunosuppressive agents during treatment of acute cardiac rejection.

Additional Aspects of Therapy During the Early Postoperative Period

During the past four years, all recipients have been placed on a continuing maintenance regimen of dipyriramole and warfarin sodium in an attempt to diminish long-term intimal proliferative responses and atherosclerosis in the coronary arteries of the donor heart. Such pathological complications were common in our early experience, and accounted for the majority of deaths in patients surviving beyond the first three postoperative months. Since institution of this regimen, the incidence of graft arteriosclerosis...
in long-term survivors has declined significantly, although it remains unproved that the above agents have been directly responsible for this improvement in late results. Other factors considered potentially important in the genesis of this complication include the severity and frequency of acute rejection injury and lipid abnormalities (see below).

Careful attention to surveillance for infection and maintenance of a semiprotective environment are initiated immediately after transplantation. Frequent cultures of urine and sputum, as well as daily chest X-ray films, are obtained. Reverse isolation technique is employed during the first several weeks after operation.

Infectious complications of immunosuppression constitute an important threat to survival of the cardiac recipient, especially during the early postoperative period, in which more frequent acute rejection episodes require periodic augmentation of levels of immunosuppression. The occurrence of infections during the first 60 days after transplantation in our series is summarized in Table 4. Surveillance for infectious complications by daily chest X-ray examination and appropriate cultures is extremely important, inasmuch as prompt diagnosis and institution of treatment are necessary to achieve survival in the immunocompromised host. Upon suspicion of a pulmonary infection, transtracheal aspiration is performed immediately. In the event of failure to establish a specific diagnosis by this technique, needle aspiration of pulmonary infiltrates or nodules is performed. The aggressive diagnosis and treatment of the frequent and serious infections encountered in our patients has contributed significantly to the survival rates attained.

Hospitalization for patients after the operation has averaged 60 days. For those who died, the range is one to 65 days. Survivors have been hospitalized 32 to 223 days, with an average of 72 days. In-patient costs for the operation and early postoperative care have averaged $36,130 per patient, with a range for the current year of $21,000 to $49,650.

Late Postoperative Management

After discharge from the hospital six to eight weeks after transplantation, continued close surveillance for evidence of graft rejection or infectious complications is maintained at regular intervals. During the first three to six months after discharge, patients are examined twice weekly, and thereafter at weekly intervals for approximately one year. After the first postoperative year, clinic visits are continued on a biweekly basis. At each visit, physical examination is performed and an interim history taken. Electrocardiograms are obtained and analyzed as detailed above. In addition, monitoring of serum electrolytes and of hepatic, renal, and hematological function is continued.

Late Acute Rejection

The diagnosis of late acute rejection episodes is based on the same criteria as outlined above. Data derived from the first 59 patients in our series demonstrate that, during the period between two and four months after transplantation, episodes of acute rejection occur at a rate of one per 160 patient days. Thereafter, this rate decreases to one episode per 200 patient days during the interval between four and 12 months postoperatively, and subsequently to one episode per 325 patient days. Electrocardiographic changes have been observed in all episodes of late acute rejection. In 90% of these there was an average 32% decrease in summed QRS voltage. Fifty-two percent of the episodes were associated with transient arrhythmias, including atrial and ventricular premature contractions and atrial flutter and fibrillation. The most frequent findings on physical examination consisted of diastolic gallop sounds (40% of all episodes). As in the early postoperative period, transvenous endomyocardial biopsy is performed in late postoperative patients upon suspicion of an acute rejection episode.

Treatment of late acute rejection episodes consists initially of an increase in the dose of oral prednisone to 1.5 mg/kg/day, with subsequent reduction to maintenance levels over the ensuing two or three weeks. During this interval, frequent electrocardiograms and physical examination are used to evaluate the effectiveness of treatment. Repeat endomyocardial biopsy is performed seven to ten days following institution of increased immunosuppression to assess the degree of reversal of histologic changes. Patients who do not respond satisfactorily to this regimen, as indicated by continuing clinical or histologic evidence of rejection, are treated as outlined above for early postoperative acute rejection.

Seventy-two percent of all late acute rejection episodes are associated with fatal outcome in our series. The mortality rate in our patients treated for rejection is 32%, which is consistent with the experiences of other investigators. There has been no mortality associated with late acute rejection in patients treated with azathioprine.

Data in Table 4 indicate a high incidence of bacterial infection early in the postoperative period. Infections are seen in 38% of our patients during the first 60 days after transplantation. Thereafter, infections decrease in frequency, and 48% of the infections occur in the first three months after operation. During the early postoperative period, the most common bacterial infection remains Pneumonia, followed by peritonitis, infection of the urinary tract, and brain abscess. A review of these infections reveals that urinary tract infection was the most common infection. Seventeen percent of these infections were due to Staphylococcus aureus, 10% to Escherichia coli, and 5% to Proteus vulgaris.

Table 4

<table>
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<tr>
<th>Infection</th>
<th>N</th>
<th>Episodes associated with fatal outcome</th>
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<tbody>
<tr>
<td>Pneumonia</td>
<td>53</td>
<td>25</td>
</tr>
<tr>
<td>Septicemia</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Brain abscess</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Disseminated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>viral infection</td>
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<td>1</td>
</tr>
<tr>
<td>Peritonitis</td>
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<td>1</td>
</tr>
<tr>
<td>Wound infection</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>86</td>
<td>41</td>
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episodes have been treated successfully on an outpatient basis with increases in doses of oral prednisone only. The remaining episodes required more aggressive therapy.

Rehabilitation and Late Graft Function

An evaluation of functional status in 32 recipients surviving at least three months after transplantation has been made. The total survival experience represented by this cohort of patients represented 50.8 patient years. Twenty-seven of the recipients had been restored to New York Heart Association functional class I, and 23 of these returned to active employment. Four, who had retired preoperatively, remained physically active and five were partially disabled. Thirty-one patients have now survived more than one year. Sixteen (52%) have returned to their preoperative occupation full time. Nine (29%) have retired but have led a normally active life. Two other patients attend school full time. Four patients have been partially or totally disabled, mainly from the complications of prednisone therapy.

The hemodynamic capacity of the long-term transplanted heart has been assessed by maximal exercise studies at periodic intervals, using an upright bicycle ergometer. Fatigue of leg muscles, rather than dyspnea, was usually the limiting factor during exercise. The maximum work load imposed, based on oxygen consumption, represented only moderate exercise as compared to normal control subjects. Heart rate responses showed an average increase from 107 to 149 beats/min, illustrating the ability of the denervated transplanted heart to increase its rate in response to muscular stress. In all cases, the increase in heart rate during the exercise period was gradual, in contrast to the abrupt acceleration observed in subjects with normally innervated hearts.

Right and left heart hemodynamic studies were performed in eight patients one year after transplantation. All of these recipients were clinically stable at the time of study, and none was receiving digitalis or other cardioactive drugs. Average pulmonary artery pressure at rest was 21/10 mm Hg, with a mean pressure of 14 mm Hg. Pulmonary vascular resistance averaged 2.1 Wood units, confirming the reversibility of pulmonary hypertension and resistance abnormalities in these recipients. Average cardiac output at rest was 4.4 L/min, and increased to 8.4 L/min after 10 min of supine, submaximal exercise. Left ventricular end-diastolic pressure, which averaged 12 mm Hg at rest, increased markedly during the initial stages of exercise to an average level of 21 mm Hg at 4-6 minutes. Left ventricular end-diastolic pressure then declined later in exercise, while both cardiac output and heart rate were still increasing. These data suggest that, during the early stages of muscular exercise, increase in cardiac output is due to an increased stroke volume secondary to augmented venous return, and possibly, decreased systemic vascular resistance. Later in the exercise interval, continuing increases in cardiac output, associated with decreases in left ventricular end-diastolic pressure, probably reflect enhancement of cardiac contractility due to circulating catecholamines. Thus, in long-term survivors of cardiac transplantation, satisfactory allograft performance has been documented, confirming the capacity for normal physical activity in such patients.

Complications and Mortality

Following Cardiac Transplantation

Table 5 summarizes the causes of death in the 54 patients who have died in this series. In common with other patients receiving immunosuppressive therapy, recipients of cardiac transplants are predisposed to infectious complications which in our experience have contributed substantially to postoperative morbidity and mortality. In the first three postoperative months infections are the most common cause of death. The lungs have been by far the most frequent site of infection and have been involved in approximately 60% of all diagnosed infections. Bacteria have been the most frequent etiological pathogens associated with a fatal outcome. In pulmonary infections developing during a period of high-dose immunosuppressive therapy, the clinical course has usually been fulminating and resulted in death, despite institution of appropriate therapy. At postmortem examination, such patients have frequently been found to be infected with multiple pathogens. Aspergillus, Pneumocystis carinii, nocardia, and cytomegalovirus have commonly been associated with bacterial pneumonias.

Severe acute rejection, unremitting despite the use of massive immunosuppressive therapy, caused the death of 12 patients. This is most common in the first three months after transplantation, and only one patient has died from acute rejection after one year’s survival. Five patients have died of complications

<table>
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<tr>
<th>Causes of Death After Transplantation</th>
<th>0-3 mo</th>
<th>3-12 mo</th>
<th>After 12 mo</th>
</tr>
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<tbody>
<tr>
<td>Infection</td>
<td>18</td>
<td>5</td>
<td>7</td>
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<tr>
<td>Rejection, acute</td>
<td>9</td>
<td>3</td>
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<tr>
<td>Rejection, chronic</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(graft arteriosclerosis)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>11</td>
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related to chronic graft rejection that produced pathological changes similar to those of advanced atherosclerosis (see below).

Three patients have died of early postoperative graft failure related to the inability of the normal right ventricle to function in the face of markedly elevated pulmonary vascular resistance. One patient died of cerebral infarction secondary to an embolus, which arose from an ulcerated arteriosclerotic plaque at the common carotid artery bifurcation. This was the only death that could not be linked in some way to the consequences of cardiac transplantation. Finally, two patients died at 7 and 21 months from apparently mixed de novo histiocytic lymphoma.

The side effects of the immunosuppressive medication required in these patients must also be considered in the discussion of complications after transplantation. Azathioprine and cyclophosphamide, however, have been associated with a low incidence of significant side effects. Four patients developed mild liver function abnormalities while taking azathioprine. In addition, other patients have developed leukopenia while on this agent. Reduction of maintenance doses in all cases led to resolution of the abnormalities. Granulocytopenia and thrombocytopenia occurred in 12 and 15 patients, respectively, receiving cyclophosphamide. Once again, reduction of maintenance doses resulted in reversal of the abnormalities.

The administration of prednisone is associated with varying degrees of osteoporosis, particularly of the lumbar spine, in nearly all patients. Aseptic necrosis of the femoral and humeral heads developed in two patients. Finally, two patients sustained perforated gastric ulcers during the early postoperative period. Both survived operative repair.

Pathology of the Transplanted Heart

The pathology of acute and chronic rejection in the allografted heart has been well characterized in both the dog and man.21-28 Serial biopsy studies and autopsy findings in animals and in man suggest that the microscopic changes of acute graft rejection can be arranged in a more or less chronological order. Endothelial swelling, accompanied by fibrin and platelet deposition, in addition to intimal and perivascular infiltration by immature mononuclear cells, as well as interstitial edema, appear to be the first histologic signs of the rejection process. Capillary rupture and interstitial hemorrhage and arterial medial necrosis then occur, and finally myocytolysis becomes significant.

The point at which acute cardiac rejection results in irreversible, lethal damage to the graft remains conjectural. It is apparent, however, from clinical experience and serial biopsy studies that in 90–95% of cases, the diagnosis of acute rejection can be made and therapy instituted early enough to prevent irreversible acute graft injury.

At postmortem examination, the rejected heart is dark red, swollen, firm and edematous. The ventricular walls are thickened, and the left ventricular lumen is commonly diminished in volume. Fibrous pericarditis is a constant finding, and subendocardial and intramyocardial hemorrhage is usually present.

Pathologic findings in chronic cardiac rejection are similar to those that occur in chronic rejection of other solid organ grafts. These changes include infiltration of the intima and perivascular space of the coronary vasculature by mononuclear cells, associated with intimal proliferation and fibrosis that results in luminal narrowing of the affected coronary artery. The intimal proliferation appears to be a relatively early phenomenon and is succeeded in later stages by progressive development of atherosclerosis in the proliferative lesion. The degree of luminal narrowing resulting from this intimal proliferation and atherosclerosis varies considerably, and in severe cases produces complete arterial obstruction. Coronary blood flow has been significantly affected in some patients, as demonstrated by ischemic changes on the exercise electrocardiogram and by coronary arteriography.

It seems likely that the initiating factor in cardiac allograft atherosclerosis is immune inflammatory injury to the intima. Other aspects of this inflammatory response include the deposition of platelet and fibrin microthrombi on intimal surfaces denuded of endothelium. High levels of serum lipids in individual patients may be a contributing factor.34, 28

The other manifestations of chronic rejection include myocyte dystrophy and interstitial fibrosis. These changes probably reflect chronic immune injury, as well as myocardial ischemia secondary to coronary artery obstruction.

Summary

Within the past seven years, the operative technique for orthotopic cardiac transplantation developed in the animal laboratory has been translated successfully to the clinical setting. The feasibility of human cardiac transplantation has been demonstrated, and its ability to prolong useful life has been documented. Moderately severe pulmonary, hepatic, and renal insufficiency secondary to preoperative cardiac failure are reversed. The transplanted heart is capable of meeting the functional demands of normal physical activity up to 77 months posttransplantation. At catheterization one year following operation, near normal cardiac outputs and pressures have been documented.
Allograft rejection in its acute and chronic form remains the single most challenging problem. The pathophysiology of acute cardiac rejection is reasonably well understood. Early diagnosis is usually possible, and presently available immunosuppressive agents allow successful treatment in most instances. In some cases, acute rejection is unremitting, resulting in graft failure and patient death. Moreover, the toxic side effects of the long-term use of current immunosuppressive agents contribute significantly to postoperative morbidity and mortality. The lesions of chronic rejection and their functional complications have been characterized. Ongoing immune injury of the tunica intima has been invoked as a possible mechanism in the production of progressive arterial narrowing by intimal proliferation and fibrosis and subsequent atherosclerosis. It is important to note that the rate of occurrence of these changes has been markedly reduced in our current long-term survivors, probably as a result of early diagnosis of acute rejection, prompt institution of therapy, and treatment with antithrombotic agents (dipyridamole and warfarin).

Currently, it appears that two factors will determine whether cardiac transplantation will have a wider application for the treatment of end-stage cardiac disease. The first, donor organ supply, emerges as a potentially limiting factor due mainly to the lack of a commonly accepted legal definition of brain death. The second is the inability to manipulate the host immune response specifically, without the production of generalized immunodepression. The impact of presently ongoing investigation of immunologic enhancement and production of tolerance on the latter problem remains to be determined.

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