Cardiac transplantation at The Cleveland Clinic Foundation: the first twenty-four months

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From August 15, 1984 until August 15, 1986 184 patients at The Cleveland Clinic Foundation were screened for cardiac transplantation, 53 were accepted, and 37 received orthotopic transplants. Recipients ranged in age from 14 to 58 years; in 60% the underlying disease was a cardiomyopathy. Follow-up was complete in all cases; the shortest period was 6 months. In the most recent of four immunosuppressive protocols, cyclosporine's nephrotoxicity has been neutralized without compromising immunosuppression. Ten patients have died, producing a one-year actuarial survival of 80.3%. Two of the early and three of the late deaths were from infections (viral, fungal, and *Nocardia*). During the first 90 days following transplantation, rejection occurred 60 times in 27 patients. No patient died or required retransplantation because of rejection. Additionally, neither malignancy nor allograft atherosclerosis have occurred. Functionally, 93% of survivors report normal tolerance for activities. Cardiac transplantation provided acceptable results for individuals who would die of otherwise untreatable cardiac disorders.

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Human-to-human cardiac transplantation, which began in 1967, incited a crescendo of activity. During the following year nearly 100 transplants were performed at numerous centers from California to India. Unfortunately this flurry of activity anteceded the solutions to such basic problems as recipient selection or rejection monitoring. At Stanford Medical Center, a devoted effort headed by Dr. Norman Shumway continued. Working both in the laboratory and in the hospital, Dr. Shumway and his colleagues

established the scientific basis for cardiac transplantation.

Cleveland Clinic surgeons performed three heart transplants in 1968. The effort, however, then lay dormant until 1984. A number of recent scientific improvements have aided the current endeavor: long-distance transport of the heart, endomyocardial biopsies, and, beginning in 1983, cyclosporine. These advantages have transformed cardiac transplantation from an experimental to a therapeutic technique, a treatment where 80% of the recipients will be alive one year after transplantation.

Methods and materials

By August 15, 1986, two years after the first transplant at the Cleveland Clinic using the recent advances, 184 individuals had been screened for possible transplantation. One hundred thirty patients were advised not to undergo transplantation. Of the fifty-three patients accepted for transplantation, eight died awaiting transplantation, three did not maintain a status acceptable for transplantation, and five received transplants after the study period ended. The remaining 37 patients who underwent cardiac transplantation between August 15, 1984 and August 15, 1986 constitute the basis of this study.

All recipients fulfilled standards of indications and contraindications for transplantation.[1] Transplantation was necessitated by either New York Heart Association Functional Class IV symptoms or the continued risk of sudden cardiac death. Contraindications embraced a variety of areas: active infection, malignancy, advanced peripheral atherosclerosis, psychosocial instability, alcohol or drug dependence, irreversible hepatic or renal dysfunction, pulmonary vascular disease, or recent pulmonary embolus. Application of two contraindications evolved: age and diabetes. Initially, age above 50 years precluded transplantation; currently, only individuals beyond 60 are excluded. Similarly, insulin-dependent diabetes originally preempted transplantation. More recently, however, patients with insulin-dependent diabetes but without evidence of retinopathy, nephropathy, or neuropathy are considered for transplantation.

Compatibility of both blood group and weight determined a donor's appropriateness. The presence of preformed antibodies, if discovered during recipient evaluation, necessitated lymphocyte crossmatching prior to donor acceptance; a re-

action between the recipient's sera and the donor's lymphocytes precluded transplantation.

Donors were selected based on the adequacy of cardiac performance; only donors with adequate hemodynamics and requiring minimal inotropic support, e.g., less than 10 μg/kg of dopamine, were considered. Clinic personnel traveled to donor institutions for all harvests. Following removal of both the liver and kidneys and administration of heparin, donor cardiectomy commenced. Preservation of the donor heart included both cold potassium cardioplegia (12 mL/kg) and externally applied ice-cold saline. Ligating both venae cavae isolated the heart from the circulation, and incising the right superior pulmonary vein and the right atrium at the junction of the inferior vena cava decompressed both sides of the heart. Transecting the great vessels and pulmonary veins as they entered the pericardium completed cardiectomy. The heart was rinsed in cold saline and stored in plastic bags within a container that was in turn transported in an ice chest, maintaining the temperature at approximately 6°C during transportation.

Implantation, using the orthotopic technique, was carried out with the assistance of cardiopulmonary bypass, moderate hypothermia (28°C), and an asanguinous prime. Recipients received cytomegalovirus-free and leukocyte-poor packed cells as needed postoperatively to maintain the hematocrit at or above 30%. Administration of plasma and platelets was determined by the adequacy of hemostasis.

All patients received cefamandole preoperatively and for the initial post-transplantation period, after which cephalexin was started and continued through postoperative day four. The only other antibiotic prophylaxis was in the form of a clotrimazole troche, which was continued indefinitely. Dipyridamole, 75 mg three times daily, was given indefinitely in an attempt to decrease the occurrence of graft arteriosclerosis.

The evolution of the protocols (*Table 1*) resulted from an attempt to maintain adequate immunosuppression while reducing the nephrotoxicity of cyclosporine. The second protocol was a brief attempt (three patients) to employ oral rather than intravenous cyclosporine. The difference between protocols one and three involved changing the infusion period for intravenous cyclosporine from bolus to continuous. Between protocols three and four, the alteration was twofold: reducing the amount of cyclosporine given

and delaying its administration until after transplantation.

The fourth protocol (*Table 2*), the current method of immunosuppression, postpones cyclosporine administration until after transplantation. Once a stable hemodynamic state has been achieved, a continuous intravenous infusion of cyclosporine, 1.5 mg/kg/day, begins. In order to obtain a blood cyclosporine level of 350 ng/mL, the amount of cyclosporine administered is gradually increased to about 2.5 mg/kg/day. In the third protocol, although cyclosporine was also given as a continuous intravenous infusion, the starting dose was greater, 3 mg/kg/day, and the targeted blood levels higher, 450 ng/mL, than in the fourth protocol. In the first protocol, patients received 3 mg/kg/day in three separate one-hour infusions, maintaining trough blood levels at 300 ng/mL. The only time patients received oral cyclosporine perioperatively, in the second protocol, an attempt was made to maintain the trough level at 200 ng/mL by administering 6 mg/kg/day in two divided doses.

By the end of the first week following transplantation, immunosuppression was similar in all four protocols. Patients received 20–30 mg daily of prednisone in addition to cyclosporine, which was administered twice daily with the dose modified to keep the trough blood levels at 250 ng/mL. Finally, all patients, except those in the first protocol, received azathioprine, 2 mg/kg daily, unless their leukocyte count decreased to less than 3000/mL, at which time the drug was withheld.

All patients remained in reverse isolation during recovery from transplantation. The availability of two laminar air flow rooms in the cardiovascular intensive care unit facilitated isolation, which was continued until after the recipient had recovered fully and all invasive devices were removed.

Patients underwent fluoroscopically guided transvenous endomyocardial biopsies twice weekly for the first two weeks, then weekly until the end of the first month. Thereafter, biopsies were monthly, at least through the third month following transplantation. Biopsy specimens were processed using routine and immunological stains and interpreted with both light and electron microscopy. The diagnosis of rejection depended solely upon the results of endomyocardial biopsies. Rejection therapy changed during the study; initially, all patients undergoing rejection re-

Table 1. Immunosuppressive protocols

Protocol, dates	Number of patients	Immunosuppression		
		Cyclosporine	Gluco-corticoids	Azathio-prine
Protocol #1 8/15/84–3/15/85	8	Preoperative intravenous bolus	Moderate	None
Protocol #2 3/16/85–5/10/85	3	Preoperative oral	Moderate	2 mg/kg
Protocol #3 5/10/85–4/14/86	19	Preoperative intravenous continuous	Low	2 mg/kg
Protocol #4 5/19/86–8/15/86	7	Postoperative intravenous continuous	Low	2 mg/kg

Table 2. Current immunosuppressive protocol (Protocol #4 from *Table 1*)

Period	Cyclosporine	Glucocorticoids	Azathioprine
Preoperative	None	None	2 mg/kg, IV
Operative	None	Methylprednisolone 500 mg IV	none
Early postoperative	1.5 mg/kg/day continuous IV (blood level 330 ng/mL)	Methylprednisolone 125 mg IV every 8 hours	2 mg/kg/day IV or po
One week postoperative	6 mg/kg/day in 2 po doses (blood level 250 ng/mL)	Prednisone 30 mg/day	2 mg/kg/day po
One month postoperative	4 mg/kg/day in 2 po doses (blood level 150 ng/mL)	Prednisone 20 mg/day	No change

ceived 1 g of intravenous methylprednisolone daily for three successive days. More recently, the intensity of methylprednisolone or prednisone treatment has been tailored to the severity of rejection: for accelerating rejection, 50 mg; for moderate rejection, 100 mg; and for severe rejection, 200 mg. The duration of therapy for rejection was three days, employing either methylprednisolone or prednisone. After the three-day treatment period, patients received their pre-rejection steroid dose without an interval of tapering.

The concentration of cyclosporine in whole blood was determined daily for the first ten days and on alternate days thereafter until discharge, using high-performance liquid chromatography, with the results reported on the same day that the specimen was obtained. The target blood levels were then approached by modifying the amount of cyclosporine administered.

Table 3. Waiting period from acceptance until transplantation

Period	Number	Days waiting	
		Mean ± SD	Range
First year	16	14 ± 11.4*	0–49
Second year	21	38 ± 25.8*	1–91
Entire period	37	28 ± 23.9	0–91

* $p < .05$ difference between mean

Results

Recipients

Of the 37 patients undergoing transplantation during the program's first 24 months, 78% were male. Cardiomyopathies had afflicted 60% of the recipients. Transplantation was required in 27% because of coronary artery disease, and in the remaining 13% because of valvular heart disease. Recipients had lived a mean of 41.8 years (ranging from 14 to 58 years) before transplantation. Recipient age, however, was influenced by the original pathology; patients with coronary artery disease were older, a mean of 52.9 years, than the others, a mean of 37.7 years ($p < .005$). Five patients had undergone previous open-heart procedures, and one patient had required a thoracotomy for cardiac tamponade.

Donors

The interval from acceptance until transplantation ranged from 0 to 91 days, with the delay more than doubling from the first year to the second year of the study (*Table 3*). In the second year, patients waited an average of 38 days for transplantation. Eight patients died awaiting transplantation; their survival ranged from 0 to 226 days. Actuarially, of those who died while waiting, 24% died before waiting 30 days, a 1% daily hazard of dying.

Ohio institutions provided 22 donors, six within the Cleveland area. The donor team performed 31 distant procurements, traveling from 40 to 820 miles, an average of 206 miles per procurement. Brain death of the donor resulted from a variety of injuries and illnesses, with motor vehicle accidents (41%) and gunshot wounds (35%) prevailing. Donors ranged from 13 to 39 years old and averaged 27 years of age. Females accounted for only six (16%) of the 37 donors.

Operation

Recipients required a mean of 100 minutes of cardiopulmonary bypass to complete the operation (range 66 to 230 minutes). Total ischemic time, the interval from circulatory arrest in the donor until restoration of coronary perfusion in the recipient, extended from 48 to 219 minutes, and averaged 123 minutes. Total ischemic time was composed of two stages: transportation time and implantation time; the implantation time was reflected indirectly in the aortic cross-clamp time, which ranged from 21 to 65 minutes (average 37 minutes).

Blood products

Only two patients, 5%, received no blood products during their hospitalization. Thirty-four patients, 92%, received a mean of 7.2 units of packed red blood cells, ranging from 1 to 31 units per patient. Additionally, 28 patients required transfusions of fresh frozen plasma and 11 recipients received platelet transfusions.

Rejection prophylaxis

With the exception of the second protocol, all protocols provided equivalent immunosuppression. The major difference among the first, third, and fourth protocols was the incidence of renal complications. Although renal dysfunction could not always be attributed to cyclosporine, the frequency of renal complications decreased as the method for administering cyclosporine improved. In the final protocol, not only was dialysis unnecessary, but also the serum creatinine levels were significantly lower (*Table 4*).

The second protocol, although not producing renal toxicity, provided inadequate immunosuppression; all patients experienced at least two episodes of moderate rejection during the first 22 days following transplantation. Maintaining adequate cyclosporine levels in patients in the second protocol was also more difficult. On the first day post-transplant, the mean cyclosporine level was 83 ng/mL, and by the third day, 205 ng/mL with a range of 121–338 ng/mL. Much less fluctuation was observed in the fourth protocol where cyclosporine levels on days one and three were 334 and 347 ng/mL respectively, with ranges of 177–497 and 169–503 ng/mL.

Rejection diagnosis

A total of 289 endomyocardial biopsies was performed on 34 patients during the first 90 days following transplantation. The mean number of biopsies performed per patient was 8.5 with a median of 8. The only complication from endomyocardial biopsy was pulmonary embolism sec-

Table 4. Frequency of rejection and renal complication in the four immunosuppressive protocols

Protocol	Number of patients at risk	Percent with moderate rejection‡	Percent requiring dialysis	Serum creatinine (mg/100 mL) mean ± SD	
				Day #3	Day #5
Protocol #1	7	43%	14%	3.0 ± 1.04	2.9 ± 1.86
Protocol #2	3	100%	0%	1.2 ± 0.06	1.2 ± 0.12
Protocol #3	19	21%*	16%	2.4 ± 1.38	2.4† ± 1.39
Protocol #4	5	60%*	0%	1.8 ± 0.99	1.3† ± 0.76

* p n.s.
† $p < .05$ for difference between mean
‡ during the first 22 days

ondary to femoral vein thrombosis in an individual requiring the femoral approach for biopsy. Most biopsies were performed via the right internal jugular vein.

Rejection

Of the 34 patients at risk, 60 episodes of rejection were diagnosed in 27 patients during the first 90 days following transplantation. The risk of rejection, however, was not evenly distributed over this 90-day period. The risk of rejection was highest during the second nine-day period, i.e., from post-transplant day 10 until 18, when 35% of all rejection episodes occurred. By the thirty-sixth day following transplant, 65% of all rejection episodes had occurred.

No patient died or required retransplantation because of irreversible rejection. In all but two episodes, rejection was reversed with the administration of steroids. In the two exceptions, one from protocol one and the other from protocol two, Minnesota anti-lymphoblast globulin was required in addition to steroids.

Survival

The status of all survivors was determined on February 15, 1987, with length of follow-up varying from 6 to 30 months. Actuarially, 80.3% of patients survived for one year (*Figure*). Although there was no statistically significant difference in survival between recipients who were over 40 years of age and those who were younger, the older group demonstrated a better survival, 81.8% vs. 72.2%.

Ten patients died during the 30 months of follow-up (*Table 5*), with infections accounting for more deaths than any other cause. Two patients succumbed to hemorrhage, one during repeat sternotomy in preparation for transplantation, and the other following implantation due to dissolution of the recipient's pulmonary artery, which was afflicted with cystic medial necrosis.

One recipient committed passive suicide by discontinuing immunosuppressives. Pancreatitis of unknown etiology precipitated pulmonary failure and death in one patient, and in one recipient pulmonary hypertension, secondary to an unrecognized pneumonia, produced failure of the donor heart soon after transplantation, despite the aid of a right ventricular assist device.

Functional status

Survival has been accompanied by normal function in 93% of patients. Of the 27 survivors, 11 (41%) have returned to work and 14 (52%) pursue activities of their choice without limitation. Two patients, although improved in comparison to their pretransplant status, continue to be limited, one from poor left ventricular function, and the other from uncontrolled obesity.

Nonfatal complications

Early but reversible failure of the donor heart occurred once when the donor right ventricle was incapable of sustaining the circulation at the end of the operation. With the aid of a right ventricular assist device, however, the right ventricle recovered two days later. The presumed cause of the isolated dysfunction of the right ventricle was myocardial contusion, although evidence to confirm this diagnosis was lacking.

Seven patients had pulmonary infections during the first 90 days following transplantation, and four of these episodes led to death, either directly or secondarily. In four instances, rejection and subsequent augmentation of immunosuppression preceded the pulmonary sepsis.

Seizures occurred in six patients; half of the episodes occurred after discharge in patients with obvious intracranial lesion. In three patients, however, the seizures occurred during the first eight days following transplantation.

Although no insulin-dependent diabetics received transplants during the period of the study,
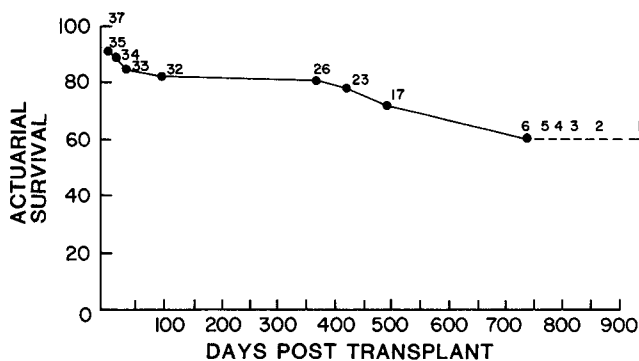
Figure. Actuarial survival for the 37 heart transplant recipients; follow-up complete through February 15, 1987.

Table 5. Post-transplantation causes of deaths

Cause of death	Patient number	Number of days posttransplantation at death
Hemorrhage	4	1
Pulmonary hypertension	35	1
Hemorrhage	37	1
Pancreatitis	27	9
Candida sepsis	29	25
Cytomegalovirus	1	73
Suicide	6	317
Aspergillus endocarditis	13	366
Nocardia brain abscess	11	429
Systemic nocardiosis	3	699

three individuals required long-term insulin replacement after transplantation. In one of the patients, cessation of insulin was possible after prednisone was reduced.

Other complications have occurred, including pancreatitis, hypertension, and an isolated cecal rupture. To date, however, none of the 27 survivors have demonstrated any evidence of malignancy.

Coronary angiography

Currently, 16 recipients who have survived for one year have undergone routine coronary angiography. These angiograms were obtained on the anniversary of the patient's transplantation, and revealed normal coronary arteries. No evidence of allograft vessel arteriosclerosis has been seen in any recipient to date.

Cost and length of hospitalization

The sum of all hospital charges from the day before transplantation until discharge or death was available for 35 patients. The median charge was $50,300, with a mean of $63,660 and a range of $16,706 to $201,183. Of the 34 patients who survived the operative procedure, the median hospital stay was 25 days, the mean stay 32 days, and the range from 9 to 85 days.

Discussion

Contraindications to cardiac transplantation have changed since the inception of clinical programs. Most recently, the utility of transplants for individuals who either are above the age of 50 or who require insulin has been explored. Centers performing cardiac transplantation are following the lead of those performing renal transplantation and are providing transplants to both older and diabetic patients. Unexpectedly, the results in our series and in that of Carrier et al[2] show that older patients enjoy a better one-year actuarial survival than their younger counterparts. Separating the effects of age and disease process, however, remains difficult, since young age is as inexorably linked to cardiomyopathy as old age is to coronary artery disease.

Unfortunately, with the recent proliferation of transplant centers, no concomitant increase has occurred in the number of donors. In addition to candidates waiting longer for transplantation, hearts are increasingly being used from donors who in the past would have been excluded from procurement. The result is an increased probability of a potential recipient dying before a donor heart is found and a decreased probability of surviving after the operation. Two solutions to the donor dilemma can be enacted immediately. Required request, which became law in Ohio in March 1987, if followed with the spirit in which it was enacted, will stimulate medical personnel to inquire routinely regarding organ donation at the time brain death is confirmed. In other states, this legislation has doubled the numbers of solid organ donations. A second solution is donor management aimed at optimizing the organ function of donors. By appreciating the pathophysiology of brain death and correcting the resultant neuroendocrine deficiencies,[3] a greater yield can be obtained from the existing population of donors.[4]

Continuous intravenous cyclosporine obviates both the erratic absorption associated with oral ingestion and the nephrotoxic peak levels following bolus injections. By delaying the initiation of cyclosporine treatment until after transplantation, the nephrotoxicity is reduced, presumably

by avoiding administration until the damaging effects of both poor perfusion and cardiopulmonary bypass have passed.

Two aspects of our protocol for treating rejection require emphasis. First, in addition to treating rejection when myocyte injury occurs, rejection is treated during an accelerating phase that includes neither myocyte injury nor an intense mononuclear cell infiltrate, criteria that are required by other groups.[5] For a diagnosis of accelerating rejection, only an increase in the intensity of the cellular infiltrate needs to be observed. Although this form of rejection may be transient ·or self-limiting, the possibility of either worsening or nonapparent injury exists. Secondly, therapy for rejection is determined only by the intensity of the rejection process and is limited to the duration of rejection. Patients, after completing the three-day treatment for rejection, return to their original, prerejection, dose of prednisone.

As in other series,[6] most deaths in our series occurred within the first three months following transplantation; seven of the ten fatalities were within 80 days of transplantation. Presently, the causes of death are too numerous to allow a sophisticated analysis to be performed; however, the potentially preventable deaths in our series occurred in recipients whose health was irreversibly compromised by their pretransplant illness or who had unsuspected sepsis. In the future, mechanical circulatory support prior to transplantation could prevent some instances of irreversible end-organ damage.

Although laminar air flow isolation cannot be proven to be beneficial, it offers protection against institutionally acquired aspergillosis.[7] Near-epidemic outbreaks of aspergillosis have been reported in some medical facilities[8]; some form of environmental isolation of the recipient seems justifiable for this reason alone. In the instance of aspergillosis in our series, the infection was acquired after discharge.

Two of our recipients developed *Nocardia* infections; both instances occurred late, both involved nonpulmonary structures (vertebral space and cerebrum), both were fatal, and only one began with a pulmonary source. These results are in contrast to a report by Simpson et al[9] of 21 cardiac recipients who developed *Nocardia* infections but without either central nervous system involvement or mortality. The seeming predilection of *Nocardia* for cardiac transplant recipients remains an enigma.

The other common complication, in our experience, was postoperative seizures. In the individuals with early postoperative seizures, two etiologies have been postulated. The first is hypomagnesemia[10]; since the last patient with early seizures, we have routinely monitored magnesium levels and corrected them when below normal. A second mechanism is an inappropriately elevated cardiac index. Since the last seizure occurred, we have given propranolol to transplant recipients who develop headache in conjunction with either an elevated cardiac index or bounding peripheral pulses. In many of these individuals the increase in cardiac index postoperatively has been 200% to 400%. The possibility of loss of cerebral autoregulation with resultant overperfusion has been considered but is difficult to prove.[11,12]

The absence of coronary arteriosclerosis may be due to the small population at risk. Several possible mechanisms, however, deserve comment. First, since rejection can manifest as graft arteriosclerosis, the most likely cause of this process would be inadequate immunosuppression. Since none of the patients in this series died of rejection, this correlation seems reasonable. The major difference between the care of these patients and those in other series has been the institution of rejection therapy prior to the occurrence of myocyte injury necrosis. Second, dipyridamole's role in preventing graft arteriosclerosis, although unproven clinically, has clear experimental benefit, as demonstrated by Lurie et al[13] in a rat model of heart transplant plus cyclosporine. Although our recipients received only dipyridamole, other groups have included aspirin,[14] a practice that theoretically inhibits prostaglandin production[15] and increases the incidence of rejection. A third mechanism, which cannot be addressed due to insufficient data, is the beneficial role of a low-animal-fat diet and careful weight control.

The cost of transplantation is directly proportional to the length of postoperative hospital stay. In the latter half of our experience, the length of stay was reduced by about 20% with a proportional decrease in hospital costs. As experience increases and postoperative complications decrease, the cost of transplantation should also decrease.

Currently, for individuals with untreatable end-stage heart disease, cardiac transplantation remains the only therapy available. While the

perioperative mortality and long waiting period for transplantation remain potential drawbacks, the frequent occurrence of long-term functional restoration to normal is gratifying.

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