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Current management of cardiac transplant recipients[1]

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SUMMARY Changes in the management of cardiac transplant recipients over the past 10 years have resulted in a substantial improvement in the outlook for survival. Imuran and prednisone remain the primary immunosuppressive agents, but rabbit antihuman thymocyte globulin is used initially and reinstituted during rejection.

Endomyocardial biopsy has allowed more precise diagnosis and management of rejection, and more recently immunological monitoring has been introduced to provide more frequent assessment of the host immune response.

Infection is the major cause of death, and its diagnosis and treatment is managed aggressively. Current survival figures justify the use of cardiac transplantation, by an experienced team, when other measures have been exhausted.

Cardiac transplantation was introduced as a therapeutic procedure 11 years ago. It was received with widespread initial enthusiasm and eventually was performed by 66 units throughout the world. Within three years of the clinical advent of heart transplantation, realisation of the complex challenges involved in the successful management of cardiac transplant recipients and the generally low survival rates achieved, resulted in the abandonment of the project in all but a few centres. At Stanford University Medical Center an active clinical programme in heart transplantation, initiated in 1968, has continued, however, and the level of activity has steadily increased. By January 1978, a total of 378 cardiac transplantation operations had been performed world wide and 97 patients were then surviving. One hundred and thirty-six of these patients had had their operations at Stanford, with 55 survivors. By the end of 1978 the total number of recipients at Stanford had increased to 161 patients with 67 survivors.

Postoperative management of the recipient has continued to evolve. Changes have resulted from both clinical experience and continuing laboratory research devoted entirely to the study of cardiac transplantation during the past 20 years. These have resulted in an improvement of one-year survival rates from 22 per cent in 1968 to 67 per cent in 1977 (the most recent year providing a minimum follow-up of one year). In this report we give an account of those aspects of treatment relevant to successful postoperative management of cardiac recipients.

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Immunosuppression

As in the case of other solid organ allografts, indefinite immunosuppression, instituted at the time of transplantation, is required for cardiac graft acceptance. The standard immunosuppressive regimen used in our programme consists of azathioprine, corticosteroids, and antihuman thymocyte globulin produced in rabbits, administered as described below.

AZATHIOPRINE

A loading dose of azathioprine (3 to 5 mg/kg) is given before operation upon confirmation of donor availability. A daily maintenance dose is then established which is the maximum tolerated without leucopenia or thrombocytopenia (usually 1·5 to 2·0 mg/kg).

CORTICOSTEROIDS

Methylprednisolone, 500 mg, is given intravenously

during operation, followed by 125 mg every eight hours for three doses. Then, upon resumption of oral intake, maintenance prednisone is started at a dose of 1·5 mg/kg per day. The daily dose is then tapered by decrements of 2·5 mg until a maintenance level of 1·0 mg/kg is reached; this is kept constant until approximately two months after transplantation when further gradual reduction of daily dose to 0·25 to 0·40 mg/kg is attempted. Both the rate of decrease of dose and the established maintenance dose of prednisone are determined by the state of graft acceptance.

ANTITHYMOCYTE GLOBULIN

Antihuman thymocyte globulin of rabbit origin (RATG) is administered immediately before operation and then daily for 10 to 14 days after operation in single doses of 2·5 mg/IgG per kg. Subsequently, reinstitution of individually prescribed courses of RATG is determined by the results of immunological monitoring (see below) and the occurrence of diagnosed acute rejection episodes. RATG is produced in the cardiovascular surgical laboratories, and current preparations may be administered either intramuscularly or intravenously. ATG produced in rabbits has, in our experience, had a greater immunosuppressive effect than similar heterologous antisera produced in horses and administered intravenously (Griepp *et al.*, 1977a).

Diagnosis of acute rejection episodes

With current immunosuppressive regimens only 10 per cent of patients have no episodes of acute graft rejection during the first three months after cardiac transplantation. The average frequency of acute rejection episodes during this time is one per 22 patient-days. Later, the frequency of acute rejection episodes decreases considerably (one episode per 325 patient-days after the first year). Effective postoperative management thus depends upon sensitive reliable diagnosis and successful management of impending graft rejection.

The clinical diagnosis of acute rejection is based upon signs that reflect impairment of graft function. Changes in ventricular mechanics caused by lymphocytic infiltration and interstitial oedema result in a decrease in myocardial compliance and contractility. A diastolic gallop rhythm (a third or fourth heart sound or both) appears early; signs of low cardiac output and congestive failure develop only with severe graft rejection. Chest *x*-ray films may show varying degrees of cardiomegaly or pericardial effusion. Changes in standard electrocardiograms include a generalised decrease in QRS voltage, a rightward shift of the mean frontal plane axis, atrial arrhythmias, and occasionally ischaemic ST-T changes (Stinson *et al.*, 1969). False positive decreases in QRS voltage may be produced by changes in impedance of the thorax, caused by pericardial fluid accumulation, pneumonia, pleural effusion, generalised oedema, and other factors. Normally, however, electrocardiographic voltage is remarkably constant, when the same machine and techniques are employed for all recordings. Measurement of serum levels of enzymes of myocardial origin is not helpful in the early diagnosis of graft rejection.

These diagnostic indices of cardiac rejection reflect already established graft damage. In recent years, therefore, efforts have been directed toward early detection of activation of the immune response by immunological monitoring and endomyocardial biopsy, in order to minimise rejection injury.

Immunological monitoring

Measurement of circulating levels of T lymphocytes (thymus derived), the putative mediators of cell-mediated immune injury, by spontaneous sheep erythrocyte rosette formation has proved to be a sensitive and useful assay for prediction of impending graft rejection (Bieber *et al.*, 1977). Since the assay can be performed daily, it provides a nearly continuous measure of the host immune status. Early postoperative administration of RATG, prednisone, and azathioprine causes profound depression of circulating T lymphocyte levels. T lymphocyte fractions less than 10 per cent (normally 65% of total circulating lymphocytes) are rarely associated with evidence of graft rejection, and therefore administration of RATG after the routine initial postoperative course is adjusted to maintain measured T lymphocyte fractions below this threshold during the first six postoperative weeks. Rises in T lymphocyte fractions above 10 per cent almost invariably herald overt graft rejection and usually occur one to three days before detectable histological changes. A major limitation of the T cell assay, however, is that after about six weeks there is no longer a close correlation between circulating T cell levels and graft rejection. Circulating T lymphocyte fractions gradually rise towards normal without subsequent graft rejection, therefore nullifying the predictive value of this assay in the later postoperative period.

Total serum rabbit globulin levels in patients treated with RATG can be serially measured by radioimmune assay (Bieber *et al.*, 1975). The data thus obtained allow characterisation of the disposition kinetics of RATG in individual patients.

During courses of RATG, serum rabbit globulin levels are inversely proportional to T lymphocyte counts; thus, low serum levels of rabbit globulin, resulting from either insufficient dosage or rapid clearance or both, are associated with an increased frequency and severity of rejection episodes and a decrease in late survival rates (Bieber *et al.*, 1977). Serial measurements of serum rabbit globulin levels are therefore used to determine both dosage and frequency of administration of RATG. Clearance rates do not remain static in individual patients, but usually decrease with repeated RATG courses (Bieber *et al.*, 1976).

Endomyocardial biopsy

The technique of percutaneous, transvenous endomyocardial biopsy of orthotopic cardiac grafts was developed in the laboratory in 1971 and applied clinically the following year (Caves *et al.*, 1973). Biopsy is performed by cannulation of the right internal jugular vein with a catheterisation sheath and passage of the biopsy forceps into the right ventricle under fluoroscopic control. Biopsies are usually performed weekly for the first six postoperative weeks, and also when impending rejection is suggested by changes in T lymphocyte levels, serum rabbit globulin levels, or electrocardiographic voltage. Because of its safety endomyocardial biopsy can be performed as frequently as indicated; early histologcal evidence of rejection can therefore be detected before development of graft dysfunction and treatment initiated before irreversible graft damage has occurred. Repeated biopsy also allows objective assessment of the response to antirejection therapy.

Treatment of acute rejection

A rise in the circulating T lymphocyte fraction during the early postoperative period is treated with increased RATG alone if biopsy fails to show histological evidence of acute rejection. If the results of biopsy are positive, however, the oral prednisone dose is increased to 1·5 mg/kg daily (with tapering to baseline levels during the ensuing two weeks) and 1 g methylprednisolone is given intravenously daily for three days. In the presence of adequate white blood cell and platelet counts actinomycin-D is given for two days in doses of 200 μg daily and heparin is administered intravenously for three to five days. Resolution of 95 per cent of rejection episodes can be expected with this treatment regimen.

Refractory prolonged acute rejection episodes are managed with additional methylprednisolone, RATG, and further treatment with actinomycin-D if tolerated. Refractory rejection is encountered most often in patients with rapid clearance of rabbit globulin, and for this reason antihuman thymocyte globulin of goat origin has recently been used in such patients. In several cases administration of rabbit and goat ATG on alternate days has resulted in reversal of apparently intractable rejection.

Chronic rejection

After the first three postoperative months the risk of acute graft rejection decreases conspicuously. Later, however, another form of graft injury may appear in the form of obliterative lesions of the donor coronary arteries. The onset of this process is insidious and its pathogenesis is probably related to antibody-mediated injury. Lesions of the coronary intima are at first entirely proliferative, but with time develop atherosclerotic characteristics. In order to assess the presence and rate of progression of such lesions coronary arteriography is performed yearly. At present, the incidence of graft arteriosclerosis, including minor disease, is approximately 35 per cent at five years. This incidence is much less than that observed in patients undergoing transplantation before 1970, when indefinite prophylaxis with an antithrombotic regimen consisting of dipyridamole and warfarin was initiated (Griepp *et al.*, 1977b). Because of its continuing occurrence, serial study is necessary, and six patients have undergone cardiac retransplantation because of critical graft arteriosclerosis. As a result of recent analysis, warfarin has not been used as an item of regular treatment since January 1979, but antiplatelet therapy with dipyridamole has been retained; other regimens of potential benefit are at present being assessed in the laboratory.

Complications of treatment

INFECTION

The majority of deaths after cardiac transplantation in the Stanford series have been the result of infection. One hundred and forty-seven patients suffered from at least one episode of infection. Pulmonary infections are the most common, and cardiac transplant recipients appear to be more prone to such infections than other transplant patients because of preoperative pulmonary congestion, thoracotomy, cardiopulmonary bypass, and endotracheal intubation. Other types of infection encountered in these patients are summarised in Table 1; blood stream, central nervous system, and urinary tract infections are also common. Because of the high incidence of infections and the broad range of both ordinary and opportunist pathogens,

Table 1 *Infections in Stanford cardiac transplantation patients*

	No. of episodes	No. of patients
Pulmonary infection	217	108
Empyema	10	10
Septicaemia	46	38
Urinary tract infection	31	22
Disseminated fungal	6	6
Disseminated viral	8	8
Central nervous system	15	15
Hepatitis	6	5
Miscellaneous	107	78
Retinitis	4	4
Osteomyelitis	1	1

Table 2 *Stanford cardiac transplantation—infecting organisms*

	No. of infections	No. of patients	No. associated with fatal outcome
Fungal			
Aspergillus fumigatus	38	38	18
Candida	9	9	4
Coccidioides	1	1	
Cryptococcus	7	7	1
Mucor	1	1	1
Rhizopus	2	2	
Yeast, unidentified	1	1	1
Nocardia	21	21	3
Bacterial			
Anaerobic mixed	34	28	5
Arizona hinshawii	2	2	1
Atypical acid-fast bacilli	9	8	
Citrobacter	4	4	
Clostridium sp	2	2	
Enterobacter	12	10	6
Escherichia coli	44	37	16
Haemophilus parainfluenzae	13	8	1
Herellea vaginicola	3	3	
Klebsiella	42	40	20
Listeria	4	4	
Mima polymorpha	1	1	
Proteus mirabilis	5	3	1
Proteus morganii	1	1	
Pseudomonas sp	24	19	8
Salmonella typhimurium	1	1	
Serratia	16	15	5
Staphylococcus aureus	26	22	5
Streptococcus pneumoniae	5	5	1
Other Streptococcus sp including enterococci	23	20	6
Viral			
Cytomegalovirus	9	9	2
Hepatitis	4	4	1
Herpes simplex	38	37	1
Herpes zoster	23	23	2
Influenza A	3	2	
Unidentified	3	3	1
Protozoan			
Pneumocystis	16	15	4
Toxoplasma	5	5	4
Trichomonas	1	1	1

diagnostic procedures must be aggressive and complete. For example, when pulmonary infection is suspected bronchial aspiration is performed as an initial diagnostic procedure. Transthoracic needle aspiration of the lung is often performed when radiological findings suggest fungal or protozoan infection or when there is any pulmonary infection of obscure aetiology.

The list of infecting agents encountered in our series (Table 2) illustrates the prominence of opportunist pathogens. Despite the severity of such infections in patients who have had large doses of immunosuppressive agents, however, rapid diagnosis and aggressive treatment have resulted in successful resolution in most cases.

MALIGNANT DISEASE

The incidence of *de novo* malignant disease after cardiac transplantation is similar in our series to that described for renal transplantation (overall 6%). Thirteen malignant lesions have been diagnosed in the total 161 recipients. These included five carcinomas (four skin, one colon), two cases of acute myeloid leukaemia, and six lymphomas. All the lymphoproliferative diseases occurred in patients whose original diagnosis was idiopathic cardiomyopathy; such patients constitute only 41 per cent of our transplant population (Krikorian *et al.*, 1978). Moreover, all have been in the younger age range (15 to 30 years). Four patients have died of malignant disease, and the remainder, including four with *de novo* lymphomas, have survived with appropriate treatment.

Outpatient care

The average hospital stay after transplantation is 55 days. After discharge patients are initially seen twice weekly in the outpatient clinic, and thereafter the frequency of outpatient examination is progressively decreased, in the absence of complications, to once monthly. Patients who remain clinically stable return after two or three months to the care of their referring physicians.

Infection and graft rejection are the principal hazards for long-term cardiac recipients. At each outpatient visit, therefore, evidence of such potential complications is sought. Physical findings suggestive of graft rejection include arrhythmias, a diastolic gallop rhythm, a pericardial friction rub, and congestive heart failure. Such findings, either alone or in association with electrocardiographic changes, may require repeat transvenous endomyocardial biopsy on either an outpatient or inpatient basis. Chest *x*-ray films and electrocardiograms are obtained, and routine biochemical tests include

measurement of serum lipids. Hyperlipidaemia, if persistent, is treated with appropriate agents.

Maintenance treatment, other than that required for indefinite immunosuppression, often includes diuretics and supplementary potassium because of the salt-retaining effect of prednisone. The initial treatment of acute rejection episodes diagnosed in the outpatient department on clinical and electrocardiographic criteria (with or without endomyocardial biopsy) generally consists of temporary increase of prednisone dosage to 50 mg twice daily, followed by a daily reduction of the dose by 5 mg to a level 10 mg above prerejection maintenance dosage. Further tapering is accomplished slowly. If complete reversal of signs of acute rejection does not occur within several days, the recipient is admitted for endomyocardial biopsy, and intravenous methylprednisolone and RATG are given as described for early postoperative acute rejection episodes. The maintenance dose of azathioprine is continued according to bone marrow tolerance.

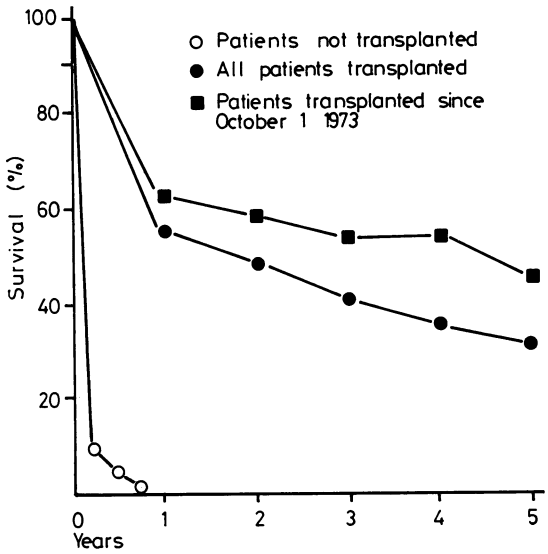

Fig. *Survival rates calculated by actuarial method for patients undergoing transplantation and for those selected for transplantation but who died before a donor could be found.*

Survival rates

Survival rates, calculated by the actuarial method, for patients undergoing transplantation and for recipients selected for transplantation but who died before a suitable donor became available are shown in the Figure.

Survival rates have improved significantly since 1973, coincident with the introduction of the endomyocardial biopsy technique in routine clinical management, the use of ATG of rabbit origin, and the refinement of immunological monitoring methods. In 94 consecutive patients undergoing transplantation since 1973, the survival rates at one, two, three, and four years were 63 per cent (±5·2SE), 58 per cent (±5·4), 54 per cent (±5·8), and 54 per cent (±5·8), respectively. These figures compare favourably with graft survival rates in recipients of cadaveric renal transplants; in most large series the one-year graft survival rate is approximately 50 per cent (Renal Transplant Registry, 1977); 90 per cent of surviving cardiac recipients in the Stanford programme have returned to full activity and the majority have resumed active employment.

Discussion

The experience described in this report has shown that cardiac transplantation can be effective treatment for selected patients with end-stage cardiac failure not amenable to treatment by any other means. Current survival figures are equal or superior to graft survival rates for renal transplants from unrelated donors. These results may encourage those in other centres to renew their interest in clinical cardiac transplantation.

It is not absolutely necessary for clinical heart transplantation to be performed in a centre with established renal and/or hepatic transplant programmes (cardiac transplantation is the only form of organ transplantation at present performed at Stanford). The diagnosis and management of cardiac allograft rejection differs from that of rejection in the case of other organ transplants, and it should be emphasised that a fully trained and committed staff accustomed to early and long-term postoperative care of cardiac surgical patients is essential for a successful effort in cardiac transplantation.

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