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Heart Transplantation. A Retrospective Analysis of the Long-Term Results

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Long-term results of orthotopic heart transplantation vary among different institutions. The purpose of the present study was to assess the factors, which might affect long-term survival and complications. Between November 1992 and July 2003, 112 heart transplantations (M/F=89:23) were performed. The standard technique was used in the first 57 patients and the bicaval technique in the latter 55 patients. Indications for transplantation in decreasing order of frequency were dilated cardiomyopathy (75%), ischemic cardiomyopathy (7%), and others (18%). The mean follow up duration was 51.8 $\pm$ 31.3 months with 98 patients remaining alive. Preoperatively, all patients were either in NYHA functional class III or IV. Postoperatively, all patients showed improvement to functional class II or I, except 3 patients that remained in NYHA class III. The mean number of rejection cases within the first year was 0.6 $\pm$ 0.8, with humoral rejection noted in 3 cases. The graft vascular disease (GVD)-free survival at 3 and 5 years was 96% and 83%, respectively. The 7-year survival after heart transplantation was 84%. There were 16 deaths, of which infection (n=4) was the most common followed by rejection (n=3), and malignancy (n=2). The present long-term results, were relatively superior to those seen in western countries. The relatively low GVD-free survival rate is thought to have contributed. The complications encountered after transplantation were mostly immunosuppressive drug related, suggesting further potentials for improvement in long-term survival.

Key Words: Standard technique, bicaval technique, heart transplantation, graft vascular disease

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INTRODUCTION

Christian Barnard's first successful orthotopic human cardiac transplantation, which was based on the seminal works of Norman Shumway, marked the beginning of the cardiac transplant era.[1] Heart transplantation has since been looked upon as a realistic option for the cure of end stage, heart failure. However, it was not until significant advances in immunology and surveillance techniques were made that cardiac transplantation truly became a practical option. Despite the advances over the years, the five-year survival rates of most large series, including those from the more successful institutions, remain at around 60%.[2] An evaluation of our experience is presented herein with the aim of identifying which factors may have prognostic importance.

MATERIALS AND METHODS

Between November 1992 and July 2003, 112

adult cardiac transplantations were performed. During this period, the first 57 patients were operated on by the standard technique while the latter 55 patients underwent the bicaval technique. The mean recipient age was 39.1 ± 13.8 (13 - 66) years, the M : F ratio was -89 : 23, and the mean waiting time was about 5 months. The mean donor age was 27.6 ± 9.2 (11 - 49) years and the M : F ratio was 93 : 19. Sex mismatch was present in 25 cases. Male to female donor-recipient matching occurred in 13 cases whereas female to male donor-recipient matching occurred in 12 cases. During the waiting period, one patient was successfully sustained on the Thoratec left ventricular assist device until surgery. The most common indication for transplantation was dilated cardiomyopathy (DCMP, 75%), followed by ischemic cardiomyopathy (iCMP, 7%) and others (18%). The only serious preoperative associated risk factors were diabetes mellitus in 8 patients and renal failure in 2. The mean follow-up duration was 30.9 ± 22.8 months (Table 1).

Table 1. Summary of Patient Demographics

Study duration	1992.11 - 2003.7
Total	112
Recipient	
Age (yrs)	39.1 ± 13.8
Sex (M/F)	89/23
Donor	
Age (yrs)	27.6 ± 9.2
Sex (M/F)	93/19
Operative technique	
Standard	57
Bicaval	55
Transplantation indication	
DCMP	83 (75%)
Ischemic CMP	8 (7%)
Hypertrophic CMP	6 (5%)
Others	13 (13%)
Associated risk factors	
DM	8
Renal failure	2
Previous OHS	6
Follow up duration (mo)	30.9 ± 22.8

DCMP, dilated cardiomyopathy; CMP, cardiomyopathy; DM, diabetes mellitus; OHS, open heart surgery.

STANDARD TECHNIQUE

In the early part of the study period from November 1992 to December 1998, all operations were performed according to the standard technique as described by Lower and Shumway.[3,4] Cardiopulmonary bypass was initiated via selective vena caval and ascending aortic cannulation. A left ventricular vent was passed through the right superior pulmonary vein. The recipient's heart was excised at the level of the atrioventricular groove and across the great vessels above the two valves. The donor heart was lowered into the pericardial well after the left atrium was opened through the pulmonary veins, and trimmed to match the recipient's left atrial cuff. The left atrial anastomosis was achieved with a continuous 3 - 0 monofilament polypropylene suture, starting at the area of the left atrial appendage and progressing down the lateral free wall. The anastomosis was completed with the other arm of the suture along the septum inferiorly. The donor right atrium was then opened in a curvilinear fashion from the inferior vena cava (IVC) to the right atrial appendage, avoiding the area of the sinoatrial node. The right atrial donor-recipient anastomosis was completed with a continuous 3-0 monofilament polypropylene suture, starting close to the IVC and continuing superiorly along the interatrial septum. The donor pulmonary artery was trimmed to the appropriate length, and anastomosed with a continuous 4 - 0 monofilament polypropylene suture. Finally, the donor ascending ascending aorta was trimmed to match with the recipient for end-to-end anastomosis in continuous running fashion with 4 - 0 monofilament polypropylene sutures. The heart was rewarmed during the aortic anastomosis. The posterior wall anastomosis was extended anteriorly and tied after air was removed from the donor heart. The aortic cross clamp was released after the donor heart was allowed to fill with blood and all left-sided air was purged through the aortic suture line. Similarly, air from the right side was purged by successively tying the superior vena cava (SVC) anastomosis and the pulmonary artery anastomosis after releasing the aortic cross clamp.

WYTHENSHAWE BICAVAL TECHNIQUE

The bicaval technique described by Sarsam and colleagues[5,6] was used from January 1999 until July 2003. Donor harvesting of the heart was usually performed in conjunction with harvesting of other organs. After a median sternotomy, the pericardium was incised in an inverted T-shaped fashion. The incision was extended along the right diaphragmatic groove just above the IVC. The pericardial reflection over the aortic arch was dissected to expose the right innominate and the left common carotid arteries. The main pulmonary artery was then mobilized from the aorta in order to pass a nylon tape over the aortic arch. The SVC was mobilized by dissecting the pericardial reflection. The azygous vein was snared with #2-0 black silk for resection and ligation at the time of extraction. Upon completion of this preliminary preparation, the mediastinum was covered until completion of liver dissection. The ascending aorta was then cross clamped followed by the immediate infusion of 2000 ml of 4℃ HTK solution. The heart was decompressed through the IVC and the right superior pulmonary vein. Once cardioplegic infusion was complete, the aortic cross clamp was removed. The azygous vein was doubly ligated and resected. The IVC, the four pulmonary veins and the SVC were successively transected. The descending thoracic aorta was then transected followed by transection of the right and left pulmonary arteries. The harvested heart was rinsed in HTK solution and transported in the same solution.

The native right atrium was excised from the recipient with a 2 to 3 cm cuff around each vena cava. The left atrial incision was carried to the base of the left atrial appendage, leaving a small contiguous margin of atrial cuff tissue all around the LA base. The donor left atrium was sutured first to the recipient left atrium with continuous polypropylene 3-0 suture (Ethicon, Inc., Somerville, N.J., U.S.A.). A left atrial vent was introduced through the right superior pulmonary vein to avoid cardiac rewarming and for later air venting. The IVC opening was then sutured to the IVC atrial cuff with continuous 4-0 prolene suture. The donor SVC was similarly sutured to the recipient SVC-atrial cuff. The great arteries were anastomosed with continuous 4-0 prolene suture in the usual fashion. Pacing wires were placed only in the presence of junctional bradycardia or complete AV block.

IMMUNOSUPPRESSION PROTOCOL

From November 1992 to June 1999, consisting of 64 cases, the preoperative immunosuppressive protocol comprised induction with cyclosporine 3-5 mg/kg and azathioprine 2-3 mg/kg PO. After June 1999, consisting of 48 cases, the preoperative immunosuppressive protocol comprised Anti-IL2 receptor monoclonal antibody (Anti-IL2 R mAb), replacement of azathioprine with mycophenolate mofetil (Cellcept) 1.5-2.0 gm PO and administration of Cyclosporin 3 mg/kg PO. Cyclosporin was withheld if serum Cr level was greater than 1.5 mg%. Intraoperatively, solumedrol 500 mg IV was routinely injected. Postoperatively, Cellcept 1-3/gm/day and Anti-IL2 R mAb were administered as scheduled to maintain the WBC count at 4000-6000/mm^3. Postoperatively, cyclosporine trough level was maintained at 300- 400 ng/dl by the EMI method during the first year and 150-200 ng/ml thereafter. Prednisone was initially given at 1 mg/kg/day and then was decreased to 0.25 mg/kg/day at 1 month and 0.1 mg/kg/day at 6 months.

INFECTION PROPHYLAXIS

Preoperatively, HBV vaccination was carried out if HBsAg was (-) and HbsAb was (-). Pneumococcal vaccination was also routinely done along with postoperative Bactrim administration throughout the first year if tolerable. Cytomegalovirus (CMV) prophylaxis with ganciclovir IV was carried out for 4 weeks if the recipient CMV was IgG (+). If the recipient CMV was IgG (-) but the donor CMV was IgG (+), IV Ganciclovir was given for 4 weeks and then switched to oral Ganciclovir 1.0 gm tid for another 2-3 months. As a final measure, influenza vaccination was performed annually.

FOLLOW UP

Rejection was monitored by regular endomyocardial biopsy and echocardiography. The ISHLT biopsy grading system was used to diagnose rejection. The rejection index was defined as the sum of each biopsy grade divided by the number of biopsies. Rejection episodes were treated with solumedrol pulse therapy and plasmapheresis in the presence of humoral rejection. Evaluation of graft vascular disease (GVD) was performed by coronary angiogram and intravascular ultrasonography (IVUS). For GVD prevention, patients were counseled to lead a healthy life style, which included adhering to a good dietary habit. In addition Diltiazem and HMG CoA reductase inhibitors was also administered to maintain a low LDL level. Follow up at the time of writing was 100% complete.

STATISTICAL ANALYSIS

All data were expressed as mean value ± standard deviation. Data were compared by means of Student's t test. Long term survivals and GVD were derived by the Kaplan Meier method. A p value of less than 0.05 was considered statistically significant.

RESULTS

The mean ischemic time was 110 ± 45 minutes and the mean implant time was 59.3 ± 7.6 minutes. The re-operation rate for bleeding was 8% (9/112). On preoperative assessment, all of the patients were either in NYHA functional class III or IV. Postoperatively, the majority of the patients were either in NYHA functional class II or I, with only 3 remaining in class III and none in class IV (Table 2). Postoperative NYHA functional class was assessed only in the surviving patients. There were 33/112 (29.5%) infection related complications, including 4 deaths; 3 due to sepsis and 1 due to pneumonia. The most frequent type of infection was bacterial pneumonia. There were 10/112 (9.0%) episodes of CMV infection, of which 5/112 (4.4%) progressed to frank CMV disease with retinitis in 2 patients, colitis in 2 and pneumonitis in 1 patient. Cerebrovascular accident occurred in 3 patients. Cerebral infarction occurred in two patients, at 7 and 7.5 years after surgery. Cerebellar hemorrhage occurred 5 years after surgery in one patient. Constrictive pericarditis occurred in 2 patients. Compressive vertebral fracture occurred in two patients and avascular hip necrosis occurred in 3 patients with one patient eventually receiving total hip replacement. There were 4 cases of malignancies; one of each of Kaposi's sarcoma and T-cell acute leukemia, both of which resulted in death, and one of each of malignant colon polyp and squamous cell lung cancer, both of which were alive at the end of the follow up.

Table 2. Comparison of Pre and Postoperative Functional Performance

NYHA functional class	Preop	Postop
I	0	68
II	0	25
III	64	3
IV	48	0

REJECTION

Diagnosis of rejection was based on endomyocardial biopsy and echocardiogram findings. With the current protocol, endomyocardial biopsy was not routinely performed beyond 2 years after transplantation. The mean number of rejections treated during the first year was 0.6 ± 0.8 (0-3). The rejections occurred at a mean of 77 days after transplantation. All episodes of rejection were successfully controlled by IV solumedrol pulse therapy. Humoral rejection occurred in 3 cases. There were 10 cases of rejection treated after the first year. In 7 the cause was poor treatment compliance. A comparison of rejection related factors between the past, and the current immunosuppressive regimens are summarized in Table 3. The number of treated rejections in the first year was significantly less with the current protocol. Likewise, both the 3-month and 1-year rejection indexes were lower with the current protocol.

Table 3. Comparison of Rejection between the Past and Current Immunosuppressive Regimens

	Past (n=64)	Current (n=48)	*p*-value
Age (recipient)	37 ± 14	41 ± 13	NS
Ischemic time	92 ± 25	137 ± 54	< 0.001
No. of HLA-matching foci	1.1 ± 0.8	1.3 ± 1.0	NS
CSA level (1 yr)	371 ± 68	315 ± 52	0.003
Treatment no.	0.7 ± 0.9	0.5 ± 0.6	< 0.005
Rejection Index (3 mo)*	0.9 ± 0.6	0.5 ± 0.4	< 0.001
Rejection Index (1 yr)	0.9 ± 0.5	0.4 ± 0.8	< 0.001
Rejection grade at 1y	1.0 ± 1.1	0.4 ± 0.8	0.006

*rejection index during the first 3 months.

GRAFT VASCULAR DISEASE

A total of 93 patients had undergone at least one coronary angiogram (CAG) and 79 (85%) of these patients received CAG more than once. CAG was performed at mean 33.0 ± 22.9 (12 - 100) months after transplantation. IVUS of the left anterior descending (LAD) coronary artery showed significant lesions (>0.5 mm) in 57/79 (75%) of the multiple CAG patients. Baseline CAG at 4 weeks in 20 patients revealed donor transmitted lesions in 9 (45%) of these patients and De novo lesion at 1 year in 4 (20%). By lesion type there were 28% and 72% circumferential and eccentric lesions, respectively, and 16% and 84% diffuse and focal lesions, respectively. The cumulative, angiographic, GVD-free survival at 3 and 5 years was 96% and 83%, respectively (Fig. 1).

SURVIVAL AND MORTALITY

There were 16 deaths in the entire series. The causes of death in decreasing order of frequency were infection (n=4), rejection (n=3), malignancy (n=2), lost to follow up (n=2), others (n=3), and one of each of GVD and graft failure. The rejection-related deaths were due to patient noncompliance. The cumulative survival after heart transplantation at 1, 3 and 7 years was 94%, 89%, and 84%, respectively,-(Fig. 2).

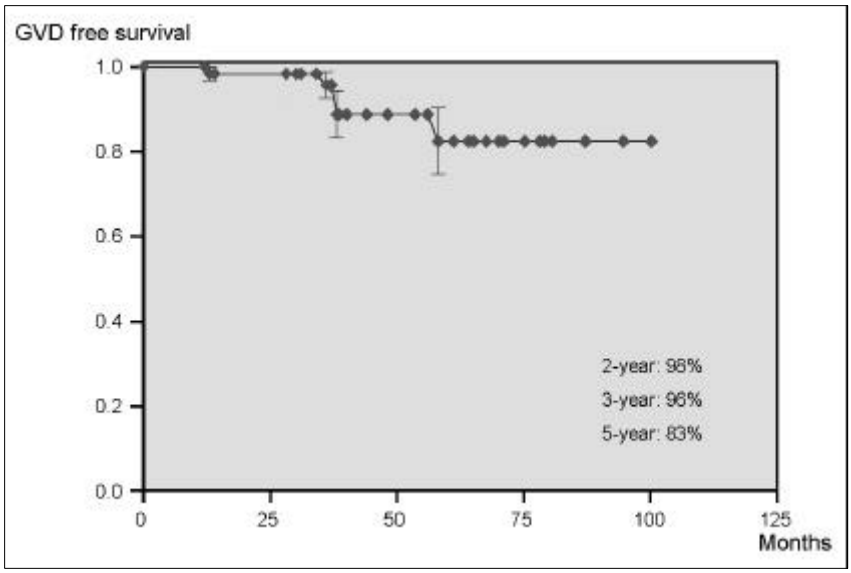

Fig. 1. Cumulative graft vascular disease-free survival curve.

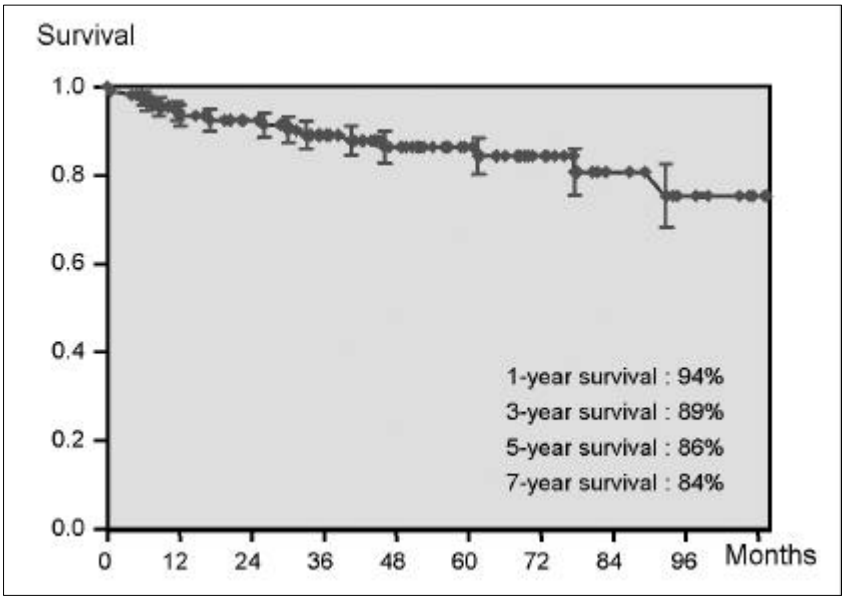

Fig. 2. Cumulative survival after heart transplantation.

DISCUSSION

Long-term analysis of the current series yielded an excellent, 7-year survival rate of 84% and an operative survival rate of 99%. This was attributable to both the consistency of surgical expertise and appropriateness of the long-term immunosuppressive and infection prophylaxis protocols. The results achieved in the present series were comparable or superior to those of other institutions-.[7,8] Of note, we experienced a very low incidence of GVD. Analysis of the 93 coronary angiograms performed revealed a GVD-free 5 year survival rate of 83% with only 1 documented death actually related to GVD. Several factors unique to our setting, as well as to our protocol, may be attributed for this favorable outcome. A strategy of very aggressive postoperative immunosuppressive protocol was instituted as soon as possible to prevent early rejection. This was based on the belief that early rejection adversely affected long-term outcome. In keeping with this strategy, the cyclosporine level was targeted at a relatively high level of approximately 400 ng/ml, provided the renal function was able to withstand the high serum level. We also noted a remarkably low incidence of CMV infection, attributed in part to the low incidence in this part of world and also to the strict and meticulous allocation of patients to specific arms of the CMV prophylaxis protocol according to the pattern of CMV specific antibody manifestation. Recently, the roles of various infectious diseases, including CMV, have been suggested to be important in the development of plaques and coronary atherosclerotic disease.[9-11] In this context, the relative absence of CMV infection may have contributed to the low incidence of GVD in this study. Furthermore, the close proximity between the referring and transplant centers may have contributed positively by allowing minimization of the ischemic time. Racial homogeneity in the study population may also have been important in reducing the GVD rate. Although rising, the incidence of atherosclerotic heart disease in Korea is still relatively low compared to western nations, and this is reflected in the patient demographics showing a predominance of DCMP as the primary indication for cardiac transplantation.

Another notable facet of the present series was the relatively low incidence of infectious complications, with only three infectious events in the early postoperative period. In the face of a relatively aggressive immunosuppressive protocol, this was a surprising finding. We believe that the various components of our overall infection prevention strategy contributed in concert to produce this favorable result. The strategy of reverse isolation, an exhaustive part of the present protocol that was instituted for the first 30 postoperative

days in all of our patients, was thought to be particularly helpful in reducing the incidence of early infection.

Seven of the deaths (n=16), were immunosuppressive drug related. Of these, the deaths caused by rejection were the direct consequence of noncompliance. A major factor for the noncompliance was the excessive economic burden from the high cost of the immunosuppressive medications, which could not be sustained by some patients.

With regards to our transplantation protocol on the whole, two major changes were made,-: switching from the standard to the bicaval technique and replacing azathioprine with Cellcept (mycophenolate mofetil). Cellcept is a relatively new immunosuppressive drug that has been extensively investigated in renal transplantation. The encouraging positive findings in relation to renal transplantation led to the careful adoption of Cellcept usage in cardiac transplantation. As past findings strongly suggested a close correlation between the incidence of early rejection and chronic rejection, it was thought that Cellcept might possibly improve long-term outcome by reducing the incidence of early rejection.[12-14] This reasoning was a strong argument for making the switch. As a result, we observed a statistically significant lower incidence of the rejection that necessitated treatment, and a lower rejection index at both 3 months and 1 year postoperatively, despite the longer ischemic time and lower cyclosporine level in the current protocol.

The bicaval technique was associated with a tendency for a lower incidence of postoperative arrhythmia and significant tricuspid regurgitation (TR). Similarly El Gamel et al.[6] observed a tendency for a lower right atrial pressure, lower likelihood of atrial tachyarrhythmias, less need for pacing, less mitral incompetence, and a lower need for diuretics with the bicaval technique. Notwithstanding, the advantages of the bicaval technique over the standard technique, as well as the implementation of Cellcept in place of azathioprine, although suggested is not definitely proved.

Finally, the current data strongly suggest that the potential recipients should be screened for socioeconomic status to determine if they will be able to sustain the high cost of the needed medications, which must be supplied in an uninterrupted manner.

In conclusion, most of the complications of the long-term surviving patients were related to immunosuppressive drug usage. The nature of GVD in this series was eccentric and focal, being somewhat different to the more diffuse nature of those seen in western countries. The current survival and angiographic GVD-free survival rates were, in general, relatively superior to the results in western countries. Bearing these findings in mind, it is our contention that there is potential to enhance the outcome of othotopic heart transplantation even further.

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