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Cardiac Transplantation

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INTRODUCTION

First successful cardiac transplantation in experimental animals was dated back to 1905 by Carel and Guthrie. Subsequently in 1933 Mann and his collegues at the Mayo clinic reported transplantation of the heart into the neck of dogs.

But the both were heterotopic cardiac transplantation procedures. The first successful experimental orthotopic cardiac transplant procedure was reported by Shumway in 1960.[1] Despite these interesting and exciting experimental procedures, it remained for Christian Barnard in 1966 to perform the first cardiac transplant procedure in man. Because of the frequency of acute and chronic rejection causing the ultimate filure of the transplanted heart, this procedure was persued in only a few centers until the introduction of cyclosporin.

Nowadays improved immunosuppressive therapy and the development of cardiac procurement and preservation provided the stimulus for initiating cardiac transplant program in a number of centers in the United States, Europe and even in Asia.

In Korea first heart transplantation was done in Nov. 11. 1992, at Asan Medical Center and 5 more consecutive heart transplantation were performed successfuly at Asan Medical Center.

CLINICAL INDICATION

The two most common indications today for cardiac transplantation include primary cardiomyopathy and end stage ischemic heart disease.[2] Primary cardiomyopathy occurs in three forms, the dilated, the restrictive, and the obliterative, of which the most frequent is the dilated form.

End stage ischemic heart disease is the result of previous myocardial infarction and poor left ventricular function. Congenital malformations represent only a small percent of patients. The recipient patient must be psychologically stable with the high probability of compliance regarding the medications and free of infection. Patients with insulin dependent diabetes are not favorable because of the risks of predisposition to infection and associated diffuse systemic vascular disease. Those patients with active peptic ulcer disease should have appropriate treatment prior to transplantation. Severe pulmonary vascular disease is a contraindication of cardiac transplantation. A normal right ventricle with usually fail when the after load is increased by pulmonary artery pressure of more than 60mmHg of systole.[3]

PROCEDURE

All the donor-recipient patients must be ABO compatible. Tissue typing has assumed greater importance in renal transplantion than in cardiac transplantation primarily because of the logistical

problems involved between the donor and recipient and the short time interval acceptable for cardiac preservation.

In view of these constraints, most centers perform only a preoperative lymphocyte cross match to exclude the presence of preformed cytotoxic andibodies in the recipient patient. Thus, HLA typing and DR typing have little place in the selection of donor-recipient combinations for cardiac transplantation. Cardiac transplantation requires careful coordination between procurement and recipient procedure. The procurement of the donor heart must be done within the time constraints of three to four hours of ischemic interval although prolonged preservation appears feasible in recent laboratory reports.

The operation on the donor heart is carried out with every efforts to limit the cardiac ischemic time to less than 4 hours.[4] During procurement of the donor heart, the recipient patient is simultaneously prepared for transplantation and placed on cardiopulmonary bypass. The donor heart is transported by cold storage.[5] Once the donor heart has been delivered to the recipient operating room, cardiectomy is carried out with an incision in the right atrium preparing a right atrial cuff. The orfices of the pulmonary veins are connected with a left atrial cuff and the pulmonary artery and aorta are dissected free from the left atrium. Right and left pulmonary arteries and aorta are dissected free from the left atrium. Right and left pulmonary arteries are trimmed to provide a wide pulmonary artery orfice near the bifurcation. The suturing of the donor heart to the recipient patient includes connecting the left atrial cuff of the donor heart to the recipient patient. The right atrial anastomosis completed in an end to end fashion. The aortic anastomosis is then completed followed by the inferior vena cava anastomosis.[4]

POSTOPERATIVE TREATMENT

1. Immunosuppressive Therapy

Current protocol of long term immunosuppressive treatment is triple therapy which consists of cyclosporin, prednisone and azathioprine.[6] In the operating room, when cardiopulmonary bypass is completed, 1g of methyl prednisolone is given. A dose of methyl prednisolone 125mg is given intravenously four hours later and then every eight hours for two more doses.[7] Cyclosporine is administered intravenously and then orally in the dosage level of 6 to 14mg per kg per day. Cyclosporine blood levels are observed every other day.[7] Prednisone is started on the first postoperative day in the dosage level of 0.5mg per kg twice daily and reduced by 0.1mg per kg per day is achieved approximately two months later. Azathioprine is begun on first postoperative day in a single oral dose of 2.5mg per kg per day. Subsequent doses are adjusted so that the total white blood count is bewteen 4000–10,000 cells per mm. The patient remains indefinitely on prednisone, azathioprine, and cyclosporine. If impaired renal function occurs during the administration of cyclosporine, the cyclosporine dosage is reduced, and OKT3 is added during the period of cyclosporine reduction. The patients remain in the cardiovascular surgery intensive care unit for two or three days, and if no complications occur, the patient is removed to the regular cardiac surgery ward with gradual ambulation following similar management to those patients following conventional cardiac surgery.

2. Diagnosis and treatment of rejection

The diagnosis and treatment of cardiac rejection is largely confirmed by the endomyocardial biopsy. The electrocardiogram has been found to be helpful in the identification of rejection in those patients receiving cyclosporine in German group.[8]

The endomyocardial biopsy is performed weekly for the first three postoperative weeks and then every two weeks for approximately six weeks. Biopsies are then obtained every three to four months thereafter. Acute rejection can usually be determined by light microscopy.

3. Treatment of rejection

Management of rejection includes an antirejection protocol of a three day course of methylprednisolone 1g intravenously per day. If the rejection process fails to respond, OKT3 monoclonal antibody in acute rejection is reported with good result and in some centers it has been used as first choice in acute rejection. Persistent of progression of acute rejection with decrease in cardiac performance required retransplantation.

4. Complications of Immunosuppressive Therapy

Large dosage of cyclosporine in excess of 15mg per kg have been associated with impairment of renal function. Similar experience has been reported with eventual development of chronic renal insufficiency. This is associated with an increase in BUN and creatinine and responds to a reduction in the dosage of cyclosporine. If the dosage of cyclosporine is not reduced, acute renal failure may develop associated with anuria persisting for 24 to 72 hours.[9] Under such circumstances, cyclosporine should be discontinued and either OKT3 or azathioprine substituted. If hyperkalemia or fluid volume overload occurs during the period of renal dysfunction, hemodialysis may be indicated. Cyclosporine is resumed when the urine volume returns to 500cc per day and the dosage gradually increased as the renal function permits.

RESULT

Early results after cardiac transplantation at Stanford University reveal 90% of patients to survive the operation and the first post-operative week. And more than 85% are alive 12months. Late deaths after cardiac transplantation are relatively few and are largely due to infection or chronic rejection and cardiac failure.

The functional status of patients following successful cardiac transplantation has been remarkable.[10] Most patients with cardiomyopathy are extremely ill prior to transplantation and appear moribund with bed rest. The patient's general state of health improves rapidly in the postoperative period when cardiac output returns to normal. In many instances cardiac ejection fraction is normal 6 to 21 months later with essentially a normal response to exercise. In some instance accelerated coronary atherosclerosis has been reported in patients after cardiac transplantation. This may be due to the humoral component of chronic rejection but also related to rapid progression of atherosclerosis. The International Heart Transplantation Registry published in May 1985 indicated a better than 80% one year graft survival with cyclosporine compared to approximately 60% graft survival without cyclosporine.

COMPLICATIONS

Complications following cardiac transplantation are similar to those of renal transplantation. Bacterial and viral infections occur more often in the early post-transplant course than after six months.[11] Bacterial infections may be related to the wound or mediastinum or may be remote and frequently have their source in the urinary tract. Pulmonary complications are similar to those noted in other immuno-suppressed patients and related to bacterial, viral or fungal infections.[12] Pneumocystitis is now much less common as a result of improved antibacterial management.[13]

HETEROTOPIC CARDIAC TRANSPLANTATION

Heterotopic cardiac transplantation involves the technique of using the transplanted heart primary as assist device for the left ventricle. In 1975 Barnard and Losman introduced the technique and have reported their results in 46 patients.

HEART-LUNG TRANSPLANTATION

Heart-lung transplantation is still in the early stage of development. This procedure developed at Stanford University has been utilized in several centers in the United States and England. Although the first experimental heart-lung transplant was reported in the 1940's, active research did not take place until the 1970's. At that time the surgeons at Stanford University achieved long-term survival in primates following heart-lung transplantation using cyclosporin. This was followed by a series of patients receiving heart-lung transplant operations reported from Stanford University by Shumway and Harefield hospital by Yacoub, with highly encouraging results.[14]

TECHNIQUE OF OPERATION

Recipients of heart-lung transplantation are those patients with primary cardiac disease associated with chronic pulmonary disease and elevated pulmonary artery resistance. The primary limitation to heart-lung transplantation is availability of suitable donors. To be a satisfactory donor for heart-lung transplantation, the lung must remain free of tracheal or bronchial infection, have excellent pulmonary function, normal gas exchange and reasonable compatability of chest size limitations, the donor is currently transported to the transplant center because of limitations of lung preservation.[14] The operation is performed at adjacent operation rooms in order to minimize the ischemic time. The donor heart-lung organs are removed after cardioplegic infusion and administration of a cold crystalloid solution flushed into the pulmonary artery.[14]

Cardiectomy and bilateral pneumonectomy are performed through median sternotomy incision during cardiopulmonary bypass. Particular attention must be given to preservation of phrenic and vagus nerves. The donor heart-lung tissue is then sutured in place connecting right atrial, aortic anastomosis and the tracheal anastomosis.

IMMUNOSUPPRESSION

The immunosuppression utilized in these patients include cyclosporine, methylprednisolone, oral prednisone, and azathioprine. The patient management is similar to the in cardiac transplantation.[15]

POST-TRANSPLANT COURSE

Originally it was thought that rejection of the heart and lungs occurs simultaneously and therefore the endomyocardial biopsy is a reasonable representation of both the heart and the lungs in terms of the immunologic response. However, recently it has been noted that the two organs do not necessary reject simultaneously for reasons that are unclear. Acute rejection is treated in a similar manner to that for cardiac transplantation. In some instances impairment of gas exchange and reduction in lung compliance may occur following heart-lung transplantation. This is managed by vigorous diuresis and fluid restriction. Recent results indicated that in a series of 15 patients undergoing heart-lung transplantation at Stanford, long-term survival has been achieved in 10 patients 3-30 months following transplantation.

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