CARDIAC TRANSPLANTATION

An Essay Submitted for the Partial Fulfilment

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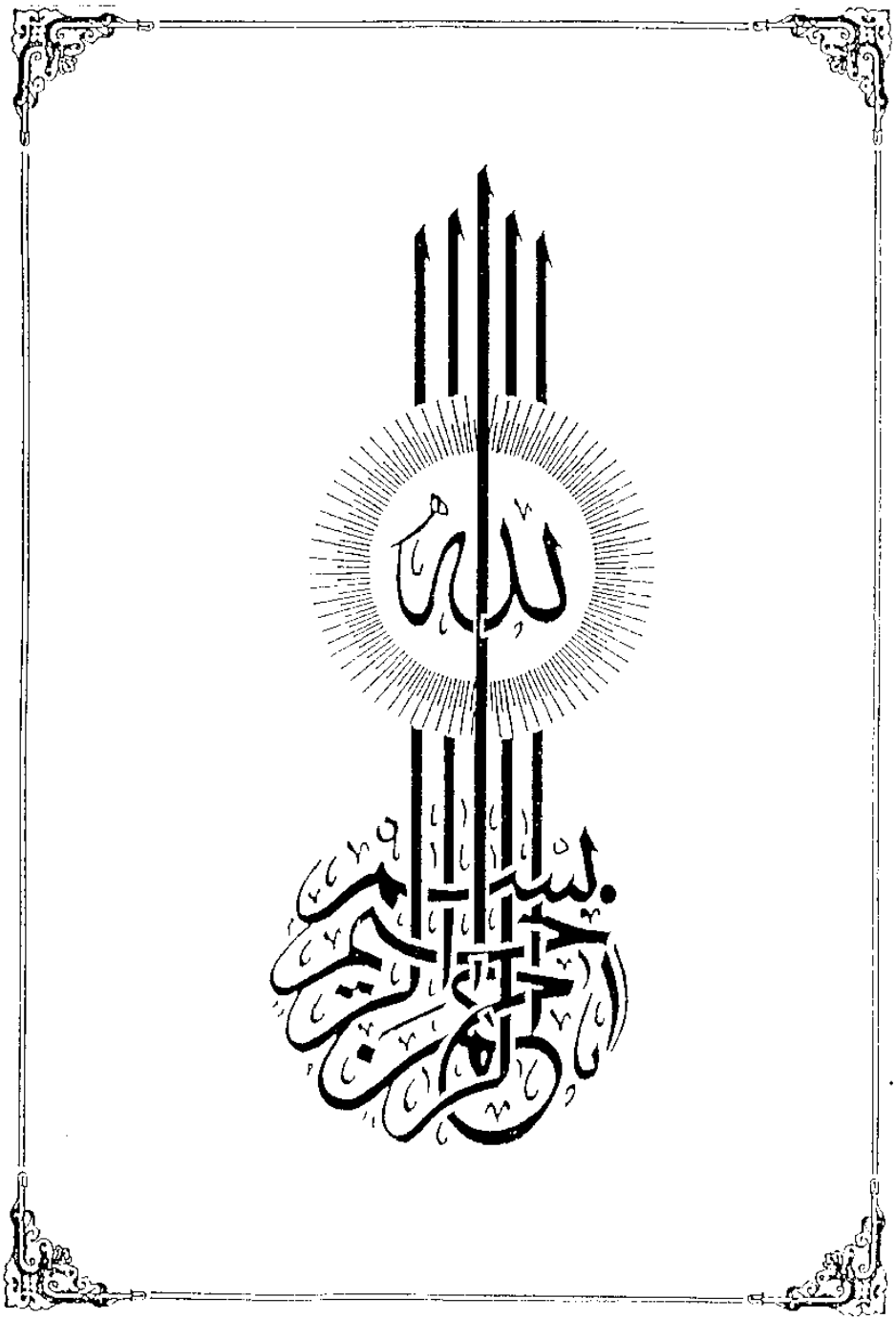

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The first report of cardiac transplantation by Carrel & Guthrie appeared in 1905.[1] Here, the heart of a small dog was transplanted heterotopically into the neck of a larger dog by anastomosis of the jungular vein and carotid artery. The heart beat for one hour.

Thirty years later, Mann et al. in 1933[2] performed a series of transplants with the intact hearts of puppies. Three times out of four, the transplanted heart resumed pulsations promptly. The average survival time of these hearts was four days and one heart survived for eight days.

Demikov in 1951[3] excised the recipient's heart with replacement by the heart of a dog. It was done without hypothermia or pump oxygenator by side to side anastomosis between the great vessels of the two hearts before the recipient's heart was removed. Demikov succeeded on two occasions to keep the transplanted heart beating for eleven and fifteen hours.[3]

Marcus et al. in 1953[4] suggested that the host heart itself might be entirely replaced. The transplanted heart would support the entire circulation. At the time, the problems faced were the support of the host

circulation during the period of cardiac excision, preservation of the heart during its extracorporeal residence and a technique for avoiding the multiple venous and arterial anastomosis, which extended the operating time and increased the post-operative intravascular clotting.

Lower et al. 1961[5] applied a successful solution to such problems by using a cardio-pulmonary bypass, local myocardial hypothermia and atrial cuffs for anastomosis. Eight orthotopic heart transplantations in dogs were done. Five animals recovered completely and lived for six to twenty-one days, then all died from allograft rejection.

Hurley et al. in 1962[6] and William et al. in 1962 demonstrated that autotransplantation of the heart could result in indefinite survival of the host and immunological problems.

The first attempt of cardiac transplantation in man was by Hardy in 1964[7] who transplanted a chimpanzee heart into a 68 year old male in cardiogenic shock. Failure of graft occured within an hour after the procedure. The first transplantation of a human heart into a human recipient was performed by Barnard in Cape Town in 1967.[7] The recipient was a 57 year old, Mr. Louis Wash Karaky. The donor's heart was an 18 year old female motor-vehicle accident victim. The recipient survived the orthotopic transplant for 18 days and then died from

acute rejection and sepsis.

Since that event the operation has been performed in many centers throughout the world. Thomson in 1969,[8] the patient lived for 19½ months but chronic rejection occured where coronary atherosclerosis developed.

In 1975. Barnard & Losman[9] successfully applied the technique of heterotopic heart transplantation. More than 15 years have passed since the first human cardiac transplantation was performed. Although heralded with enthusiasm and the performance of approximately 150 transplant procedures over the next two years, early experience was largely unsuccessful.[10-12]

Indeed, throughout most of the subsequent decade, clinical heart transplantation programs were limited to a few centers, where persistent effort led to an evolutionary development of procedures and improved results.[13-18]

Heart transplantation is now attracting renewed interest. Until May 1st, 1983 a total of 263 transplants had been carried out at Stanford University Medical Center, where experience with cardiac transplantation has been extensive. 107 out of 263 are survivors and the longest survivor is 13.3 years. The one-year survival rate is 82%.[19]

Until January 1st, 1982 at least 664 patients had undergone cardiac transplantation throughout the world, with slightly more than a third of these procedures being performed at Stanford Medical Center.[19]

INDICATIONS OF CARDIAC TRANSPLANTATION AND SELECTION OF PATIENTS

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Patients to be considered for cardiac transplantation have to be clearly defined to prevent unsuitable patients being given false hope and being subjected to a prolonged surgical procedure, including the long waiting period of preoperative assessment and the protracted post-operative care.

The operation is costly in terms of money and time and still has a high mortality rate.[20]

The main indications for cardiac transplantation are end stage coronary artery disease and end stage congestive cardiomyopathy.[21, 22, 23] The patients chosen are those whose disease is muscle disease, either primary cardiomyopathy or secondary to coronary artery disease.[24]

Coronary heart disease is the most fatal disease in industrialised countries and despite the advances in therapeutic methods, there are still patients whose disease is no longer amenable to any conservative or conventional surgical therapy. After screening for the well defined contraindications, these patients should be considered candidates for cardiac transplantation.[22] Younger aged patients are suitable candidates, and better results of such procedures is seen if the history of

these patients is relatively short and the impairment of cardiac function affects mainly the left ventricle. In this case, there is only slight degree of renal and hepatic congestion or none. This makes the post-operative immunosuppressive treatment with Cyclosporine A easier and more reliable.[22]

The majority have coronary artery disease with extensive loss of left ventricular myocardium due to multiple coronary artery occlusions. They remain Class IV cardiac status with inability to work. Bed rest is required despite optimal medical treatment and there seems to be no alternative therapy.[25, 26, 27]

A trial was done between August 1981 and August 1983 on five patients with end stage coronary artery disease who underwent cardiac transplantation.[22] Their mean age was 40 years, and all had extremely impaired left ventricular function with ejection fraction 20.2% and cardiac index = 1.6 litres/min/m^2. All had clinical severe myocardial infarction. Left ventriculography showed remarkable segmental contraction abnormalities.[22] Cyclosporine A was used as immunosuppressive in a dose of 18 mg/Kg b. wt before operation[22, 28] and adjusted according to hepatic and renal function and by radio-immuno assay to a level of 100-300 ng/ml, which is considered the proper therapeutic level.[22, 29]

Biopsies were taken, eight early rejections in the first 60 post-operative days, and one late rejection

which were all treated. There were infections with herpes virus legionella, exacerbated T.B. Psychosis and mononeuritis were two other complications. All patients lived, one lived 25 months, others 13, 10, 6 and 3 months.

There was another group of patients who suffered fewer complications,[30] accordingly, their survival rates were better. The possible causes of these better results were: the history of these patients was relatively short and as impairment of cardiac function affects mainly the left ventricle, therefore there is only a slight degree of renal and hepatic congestion or none; this makes the post-operative immuno suppression treatment with Cyclosporine A easier and more reliable.[22]

At the University of Michigan Medical Center, three male patients aged 50, 39 and 43 with idiopathic cardiomyopathy underwent cardiac transplantations. The disease was in end stages, no longer responding to medical management and no other surgical procedures were possible. All patients were so ill that they could not walk more than a few steps and could not safely be discharged from the hospital for even two or three month periods. Their cardiac catheterisation revealed severe congestive heart failure with significantly increased pressures in all heart chambers and very poor left ventricular functions.[31] One of the patients had positive family history, suggesting a familial type of cardiomyopathy. The ventricles were greatly enlarged in all three patients. Their weights were 533, 476 and 572

grams with extreme hypertrophy and endocardial scarring and some coronary atherosclerosis. The cardiac output was less than 1 litre/minute, which increased after cardiac transplantation to 5-6 litres/minute.

Histocompatibility studies were performed by Dr. Paul Terseki tests. They were performed for ABO red-cell compatibility and lymphocyte antigen matching.

Immunosuppression was carried by thymectomy, carried out at the time of cardiac transplantation. Azathioprine and prednisone was started 12 hours before the operation, continued three weeks after operation and then reduced. Heparin was also given on the fourth post-operative day and continued for six weeks, then maintenance with coumadin.

The results were excellent in terms of haemodynamics improvement and general physiologic well-being. The patients developed normal resting cardiac output of 5-6 litres/minute. Cardiac output in one patient increased with exercise with both an increase in heart-rate and exercise stroke volume.

One patient developed a rejection episode three months after cardiac transplantation, but was treated successfully with 1 gram of antithymocyte globulin and intravenous heparin.

One patient had lowered blood pressure to 20 mm Hg two hours after removing the cardiopulmonary bypass. Emergency administration of isoproterenol was necessary to restore heart-beat and cardiac output. In the subsequent

patients, the drug was given prophylactically for 48 hours and these patients did not experience similar post-operative difficulty.

One patient developed infection with pseudomonas in the right pleura, mediastinum and right lung and treated with chest drainage, colistin amd pseudomonas immunoglobulin.[31]

In 1973, Barnard observed that from 1967 to 1971, only five out of 35 patients with cardiomyopathy who underwent transplantation lived beyond the first year.[33] The proportion of patients undergoing tranplantation due to cardiomyopathy has increased in recent years. Also the post-operative management of the cardiac transplant patients has advanced greatly in the last decade.[34, 35] For these reasons, it has become important to determine whether patients with cardiomyopathy undergoing transplantations behave differently from those whith other cardiac disorders, such as ischaemic heart disease; and at what point in the natural history of cardiomyopathy should cardiac transplantation be considered.[36]

In recent years, end stage congestive cardiomyopathy has become an increasingly frequent clinical diagnosis in candidates for cardiac transplantation.

Forty-six patients underwent transplantation because of congestive cardiomyopathy and fifty-nine because of coronary artery disease, between 1971 and 1978 at Stanford University.

The age of those 46 with cardiomyopathy ranged between 14 and 64, with a mean of 38 years. They were in NYHA Class IV, suffering from rest dyspnea, orthopnea and paroxymal nocturnal dyspnea. Chest pain was present in 37% of cases, peripheral oedema and syncope in 15% of cases. There was a history of alcohol intake in 15% and positive family history in 37% of cases

Their $\frac{\text{LVESP}}{\text{LVEDP}}$ was 99/25, cardiac index 1.7 ± 0.1 lit/min/m^2 and fractional shortening F.S. 10.6 ± 0.6 and left ventricular internal diameter at end of diastole 6.7 ± 0.3 cms.[36]

The three-year survival for cardiomyopathic patients who underwent cardiac transplantation since 1974, was 60% and the overall one-year survival rate was 64%; from 1977 to 1978 it was 69%; from 1974 to 1976 it was 68% and from 1971 to 1973 was 50%.[36]

The rehabilitation of long term cardiac transplant survivors was relatively successful, as 80% of patients in the cardiomyopathy transplant group surviving the first three post-transplant months returned to NYHA functional Class I; 90% of long term survivors returned to normal physical activity, assuming employment, choosing active retirement or entering school.[36]

Patients with congestive cardiomyopathy who did not undergo cardiac transplantation have three-year survival rate of 4% and one-year survival rate of 23%.[36]