# The First Successful Heart Transplantation in Turkey

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The first reported cardiac transplantation was performed in Alexis Carrel's laboratory, in 1905, which was a successful canine heterotropic (piggy-back) operation. There was gradual improvement in surgical technique during the following decades. Clinical aplication became feasible following a series of eight canine orthotopic transplantation procedures by Lower and Shumway in 1960. On December 3, 1967, the first successful clinical cardiac transplantation was performed by Barnard at the Groote Schuur Hospital in Cape Town, South Africa. Others followed this application. Shumway performed the first cardiac transplant operation in the United States, in January 1968, which was followed by Cooley, in May 1968. By the end of 1968, 102 heart transplantations had been performed in 17 countries.

In Turkey, the first cardiac transplantation was performed by Kemal Bayazıt on 22 November 1968, at the Yüksek İhtisas Hastanesi, and four days later the second cardiac transplantation was performed by Siyami Ersek at the İstanbul Göğüs Cerrahisi Merkezi. Both patients died in the early post-operative period.

Due to rejection and infection problems, several institutions ceased to perform heart transplantations on humans. Shumway and colleagues at Stanford, however, maintained their interest, performing 227 cardiac transplant procedures in 206 patients from January 1968 to April 1981.The diagnosis of cardiac allograft rejection was greatly advanced by Philip Caves, who developed a bioptome for obtaining repeated transvenous endomyocardial biopsies, and by Margaret Billingham, who described a histological system for classification of rejection in these specimens. However, generally poor clinical results throughout the world led to a precipitous decline in interest during the following years. After more than 10 years of improvement, heart transplantation now offers a better life expectancy and quality of life to the patients severly limited by cardiac disease. One of the most important factors in the wide application of heart transplanta-

tion since 1980, has been the introduction of cyclosporine-A as the main immunosuppressive agent. Its use combined with increased experience has enabled most centers to offer 80 per cent survival.

It is now apparent that heart transplantation is no longer an experimental procedure, but rather a highly effective mode of therapy for the treatment of end stage heart disease. More than 3623 heart transplantation procedures have been performed and reported to the Registry of the International Society for Heart Transplantation during the past 5 years. In 1987 approximately 2200 transplantations were performed world wide[7].

We are reporting the first succesful heart transplantation case in Turkey, performed on September 7, 1989 at the Koşuyolu Heart and Research Hospital.

**Preoperative Evalutation**

The patient was a 58 year old male. He was admitted to our hospital in June 1989, with anterior chest pain and dyspnea complaints which had started 4 years ago. In 1987, he had a myocardial infarction and was treated in different hospitals in Ankara and İstanbul.

He used to drink a 35 cc bottle of alcohol and smoked a pack of cigarette daily for the last 30 years.

On examination, his heart rate was 90 beats per minute and regular, the blood pressure was 110/60 mmHg.

He had a grade of 2/6 pansystolic murmur heard at the apical region.

The electrocardiogram showed evidence of anterolateral ischemia, previous inferior MI, and left ventricular hyperthrophy. Chest X-Ray showed left ventricular and atrial hyperthrophy with pulmonary congestion.

Biochemical and hematological laboratory results were in the normal range.

On July 4, 1989 a coronary angiography and left ventriculography were performed. The coronary angiography showed total obstruction of the left anterior descending coronary artery. There was a severe stenosis at the circumflex artery posterolateral branch. The right coronary artery was dominant and there was a severe stenosis just before the acute margin.

The distal artery was opacified by retrograde and collateral flow, and appeared very small.

The left ventricular cavity was large, the segmental movements were severely hypokinetic, the septum was akinetic, and overall left ventricular function was impaired.

There was evidence of mitral insufficiency due to posterior leaflet prolapsus. LVEDP was 35 mmHg.

Preoperative echocardiography showed global ventricular dysfunction and ejection fraction of 20 %.

The serological test results were as follows: HTLV III (-), Hbs AG (-), CMV (cytomegalovirus) IgM (-), IgG(+), Herpes simplex IgM (-), IgG (+), EBV (Ebstein-Barr virus) (-), Toxoplasmosis (-).

His condition deteriorated progressively. He had spent most of his time in the hospital and he was included in our heart transplantation program. After awaiting a donor for a long time a suitable donor was found from the Haydarpaşa Numune Hastanesi.

The donor was 20 years old, had irreversible brain damage resulting from gun shot, and was declared le-

gally brain-dead in accordance to state transplantation protocol.

The approval from the family and legal permission from the public prosecutor were obtained and the donor was transferred to the Koşuyolu Heart and Research Hospital.

Immunological studies were performed in cooperation with the Transplantation Department of the İstanbul University Medical School.

**Surgical Procedure**

On-side donor and recipient patients were transported to the operation room simultaneously. Recipient and donor were then prepared and draped.

The heart transplantation procedure was performed by the standard method as previously described(Fig. 1).

The donor heart was cross-clamped and arrested with St. Thomas II cardioplegic solution before removal. The heart was then trimmed, passed through 2 bowls of cold Ringer's solution and finally placed in the last sterile bowl containing cardioplegic solution for transport to the adjoining operating room.

The recipient heart was excised during the cooling period. The heart was removed initially by incising into the right atrium and extending this incision inferiorly towards the coronary sinus and superiorly towards the roof of left atrium. The left atrium was then opened and the incision continued along the interatrial septum and toward the base of the left atrial appendage. The aorta was transected above the valve comissures, and then, the pulmonary artery was transected at the same level. The heart was removed by completion of the left atrial incision.

The donor heart was then placed on the operating table and implantation was begun with anastomosis of the left atrium. The left atrial anastomosis was accomplished by using a continuous 3-0 monofilament polypropylene suture, initially along the free border and then along the interatrial septum.

The right atrium was then similarly anastomosed by using the same suture, initially along the interatrial septum and then along the free border of the right atrium.

The pulmonary artery was anastomosed with a continuous 4-0 polypropylene suture. Then the aortic anastomosis was performed using the same suture. Rewarming was commenced when about half way through the aortic anastomosis. A small catheter was placed in the right superior pulmonary vein for left atrial pressure monitoring and for removing intracardiac air. Air was repeatedly evacuated from the pulmonary veins, the apex of the left ventricle, all the cardiac chambers and from the aortic root through the suture line. The aortic clamp was slowly released and the heart was defibrillated. When the patient reached 37 °C, isoprenaline infusion of 5 micrograms/min was begun. Bypass was discontinued slowly with monitoring of both filling pressures. Temporary pacing wires were placed on the right ventricle and the right atrium.

**Patient Management**

The patient was kept in a room with laminary flow for two weeks after operation.

The room and patient's bed were cleaned with antiseptic solution and sterile linen was used. The entrance of

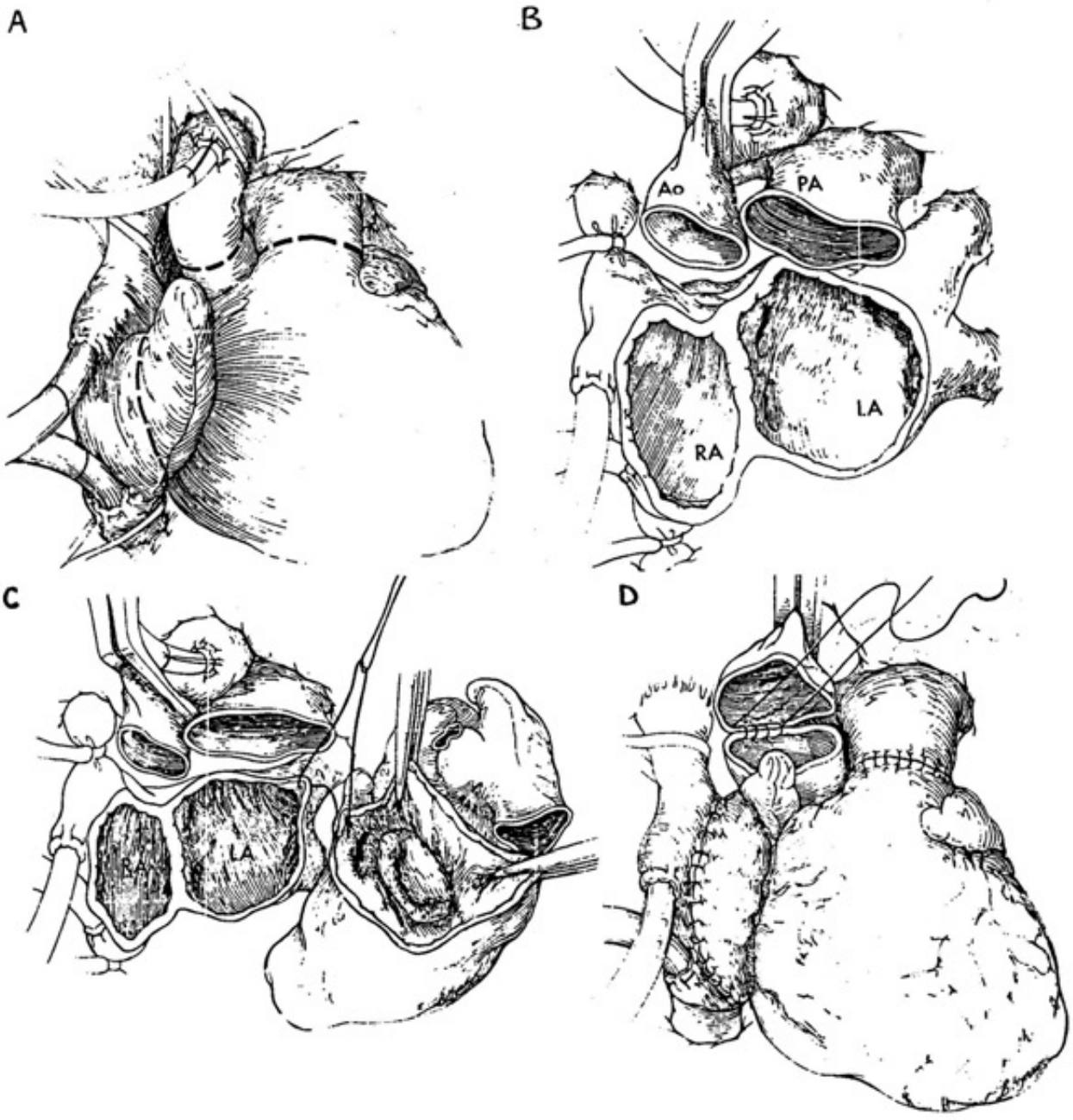


**Fig. 1:** The technical operative steps in cardiac transplantation (Reprinted from Papworth Hospital's brochure).

hospital personnel and visitors into the patient's room was restricted.

Medical personnel entering the room had to dress properly with a mask, overshoes, and gown.

Maximum care was given to provide asepsis for all medical procedures and dressings. All invasive lines were removed as early as possible; the patient was extubated the following morning, the Swan-Ganz catheter was removed on the second day, and on the third day central venous access lines were removed.

**Table I:** Immunosuppressive protocol

| | **RATG** | Cyclosporin-A | Azathioprine | Intravenous methyl prednisolone | Oral prednisolone |
|---|---|---|---|---|---|
| Preoperative | ..... | 2,5 mg/kg/oral | | | |
| Perioperative | 2,5 mg/kg/day | ..... | 3 mg/kg iv | 500 mg before starting ATG 500 mg post-bypass | |
| Postoperative | 2,5 mg/kg/day | 3-5 mg/kg/day | 2 mg/kg PO | 125 mgx3 | 1→0.2 mg/kg/day |

Double antibiotic prophylaxis with cefotaxime and mycacine was used and this application was stopped on the fourth postoperative day due to changes in renal function.

The first three days after the operation amphotericine-B was given against candida and aciclovir (Zovirax) was given for 5 days against viral infections.

Bacteriological swabs (nose, throat, atrial wires site, sputum) were performed regularly.

5 mg/min iv Isuprel was given in order to keep the heart rate between 100-110 beats/min, and stopped in the first postoperative day.

The patient did not need inotropic or pace maker support. Although rare premature beats occured, no treatment was required. Hypertension was controlled by diuretics and nifedipine.

The patient developed steroid-induced diabetes mellitus after transplantation. The blood sugar was controlled by adjusting NPH insulin dosages.

Blood investigations for virologic examinations (CMV, herpes Simplex, EBV and toxoplasma) were repeated weekly.

**Immunosupression**

The immunosuppression was based on cyclosporine, azathioprine and low dose steroids with an initial 3 days course of ATG (Table I). We based this policy on the results of the Papworth Hospital.

The patient had a moderate degree of nephrotoxicity exhibited in the early postoperative period by a rise in serum urea and creatinine levels. This early acute renal impairment resolved spontaneosly within 2 to 3 days in response to appropriate adjustment of cyclosporine-A dosage. Our patient had normal renal functions preoperatively.

First an endomyocardial biopsy was performed 9 days after the operation. The routine cardiac biopsis continued after 3,5,9,12 weeks

Right ventricular endomyocardial biopsies were performed by using the transvenous percutaneous technique. Under local anesthesia with lidocaine the right internal jugular vein was entered percutaneously. A 9 F sheath was inserted through which a cardiac bioptome (GE Yacoub model) is introduced and directed under fluoroscopy toward the interventricular septum and right ventricular apex (Fig. 2). All

**Fig. 2:** Right ventricular endomycordial biopsy by the transvenous technique. Cinefluoroscopic image of the bioptome within the heart.

biopsy sections were stained with hematoxylene and eosin, masson trichrome, methyl green pyronine, and PTAH stain in the Patology Clinic of the GATA Medical Faculty. The biopsy specimens were prepared and interpreted according to the classifications of Billingham.

Three rejection episodes occured within the first 6 weeks of transplantation, and all were moderate (Fig. 3). All rejections were successfully treated. Two early moderate rejections with myocyte necrosis were treated with pulse therapy of 1 Gm methylprednisolone given intravenously (IV) daily, for 3 days. Last, the moderate rejection episode was treated with a five-day course of rabbit ATG (2,5 mg/kg).

There was no acute rejection in the last 2 biopsies (Fig 4). In three echocardiographic observations performed monthly, ventricular dimensions, wall thicknesses, and ventricular functions were definitely normal.

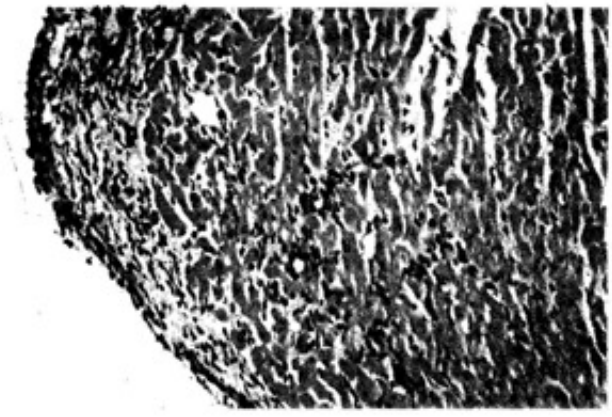

**Fig.3a:** Perivascular lymphocytic infiltration.

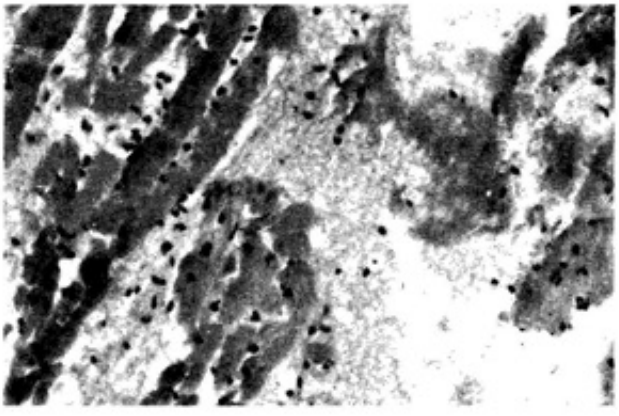

**Fig. 3b:** Myocytolysis, interstitial hemorrhage and mononuclear infiltration.

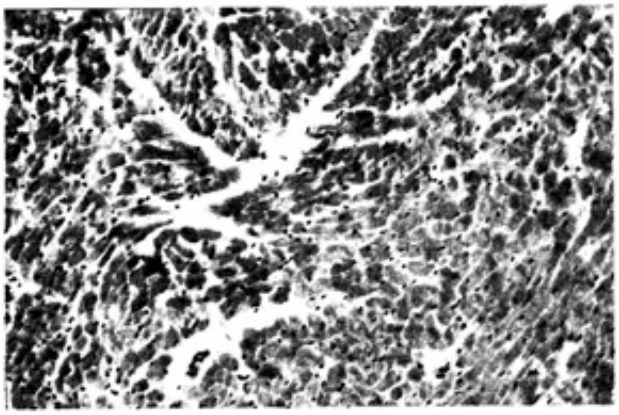

**Fig. 4:** Normal (absence of rejection).

## Discussion

Major advances have occured in heart transplantation over the last 10 years. These changes are due to better recipient selection, donor evaluation and immunosuppressive medications. Immunosuppression for cardiac transplantation has undergone a series of modifications, the most remarkable one was the introduction of cyclosporine-A in 1980 by the Stanford Group. Cyclosporine has improved the results for heart transplantation patients. However, renal toxicity, especially in the early postoperative period, has a significant effect on the long term prognosis for the patient with a transplant. High incidence of kidney failure in patients receiving cyclosporine have been described in the literature. In an effort to decrease the possibility of renal toxicity with the use of cyclosporine, we use low-dosage cyclosporine together with azathioprine, antithymocyte globulin, and tapering dosages of steroids as an immunosuppressive regimen.

The early function of the transplanted heart has been satisfactory. However, a longer follow-up is necessary to reach a more definite conclusion.

Cardiac transplantation has become a common and accepted treatment method for selected patients with severe heart failure. The primary factor that limits the number of heart transplantation in our hospital is the shortage of suitable donors. Although 44 patients are currently candidates for cardiac transplantation, only one donor heart has been available for these patients.

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