Clinical Research

Orthotopic Heart Transplantation: Early Clinical Experience and Results of a New Transplantation Centre

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Key words:
Congestive heart failure, transplantation.

Introduction: Heart transplantation is the best therapeutic option in selected end-stage heart failure patients.
Methods: We present our initial clinical experience with 22 patients who underwent orthotopic heart transplantation at our Center in the last 7 years.
Results: Total mortality was 13.6%, similar to that reported by other experienced Centres abroad. We observed a low complication rate and a satisfactory functional recovery.
Conclusions: The meticulous selection of donor and recipient and the continuous, close follow-up of patients by an experienced team, render heart transplantation a realistic and safe therapeutic modality in Greece. The low organ donation rate requires further collaboration between the responsible organizations, combined with the education of all professionals involved, as well as the Greek population.

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Congestive heart failure, a clinical syndrome caused by a variety of cardiac and non-cardiac causes, carries a poor prognosis. In most patients it is due to severe reduction of left ventricular contractility accompanied by diastolic dysfunction[1]. In spite of the salutary effect of newer drugs on survival and quality of life, the number of patients with congestive heart failure keeps climbing[2]. This may be due to an aging population, the increased use of thrombolytic agents in the setting of acute myocardial infarction and the widespread use of drugs for the treatment of heart failure[3]. Cardiac transplantation remains the main therapeutic modality for patients who are not candidates for conventional surgery and despite maximal medical treatment are plagued by symptoms[4]. In this paper we present the initial experience at the Onassis Cardiac Surgery Centre on patients with end stage heart failure treated by orthotopic heart transplantation.

Methods

Between April 1995 and February 2002, twenty-two (22) orthotopic transplants were performed at the Onassis Cardiac Surgery Centre. During the same period 532 patients were referred for opinion and 223 of those were admitted for pretransplant evaluation. The majority (309 patients) were found unsuitable, either due to early referral or because they presented obvious contraindications. The pretransplant evaluation consisted of a detailed clinical examination along with an ECG, echocardiographic study, right and left cardiac catheterization, spirometry with MVO2 determination, myocardial

viability studies (in patients with coronary artery disease), a myocardial biopsy (if indicated), pulmonary function tests and evaluation of organ systems by specialists (G.I., Nephrology, Neurology, Psychiatry, Vascular Surgery, Endocrinology, Oral Surgery, Rheumatology, etc.)[5]. The patients had a full hematology and biochemistry screening, a coagulation profile and immunological studies, HLA tissue-typing and a P.R.A. determination. From 1995 up to July 2002 a total of 150 potential recipients were checked. All studies were performed during hospitalization (5-8 days) under the supervision of two trained transplant coordinators. Data obtained were presented to the Patient Selection Committee (P.S.C.) for decision and subsequent listing. This consists of all physicians participating in the pre-transplant evaluation including the transplant coordinators. Of the initial group of 223 patients only 96 completed the pre-transplant evaluation and were presented to the P.S.C. Seventy-one patients (74%) were accepted and listed, while the remaining 25 (26%) were turned down due to contraindications.

Table 1. Baseline clinical and hemodynamic characteristics of the transplanted patients (%).

Number of patients	22
Age, year (range)	42.5 (15-60)
Gender M/F	16/6
Etiology of congestive heart failure	
Ischemic	6 (27%)
Non-ischemic	16 (73%)
NYHA functional class	
III	18 (82%)
IV	4 (18%)
Max O_2 consumption (mlO_2/kg/min)	11.7±2.3
Left ventricular ejection fraction	18%±4%
Medical therapy	
Diuretics	22 (100%)
ACE inhibitors	15 (68%)
Angiotensin Receptors inhibitors	5 (23%)
Digoxin	20 (91%)
B-blockers	11 (50%)
Amiodarone	13 (59%)
Implantable Cardioverter Defibrillator	5(23%)
Preoperative IABP	3 (14%)
Home inotropic support	9 (41%)
Hemodynamic parameters	
Mean pulmonary artery pressure (mmHg)	35.2±9.6
Pulmonary capillary wedge pressure (mmHg)	26.9±8.7
Transpulmonary pressure gradient (mmHg)	8.3±4.8
Pulmonary resistance (Wood Units)	2.0±1.41

Results

All transplant patients presented with symptoms of severe congestive heart failure due to marked left ventricular dysfunction. In thirteen patients the disease background was dilated cardiomyopathy, in six extensive C.A.D. with poor myocardial viability and in the remaining three valvular disease. Four patients had previously undergone open-heart surgery through a median sternotomy. The pertinent clinical and hemodynamic findings in these patients before surgery are presented in table 1.

Selection criteria for transplantation

The transplantation team at the Onassis Cardiac Centre follows the guidelines of the International Society of Heart and Lung Transplantation and those of the American College of Cardiology[5]. In summary, appropriate candidates for transplantation are those who are younger than 65 years of age, in end-stage cardiac failure (Class III-IV of N.Y.H.A.), who cannot be treated by conventional surgical methods while receiving maximal medical treatment. In addition, their organ systems are intact and they are free of recent infection. They should be compliant, possessing a supportive social environment and not substance dependent (including nicotine). Special attention was paid to the assessment of pulmonary circulation, which can be involved early in the clinical course as manifested by pulmonary hypertension. Significantly, non-reversible pulmonary hypertension constitutes an absolute contraindication to orthotopic heart transplantation because of the high possibility of early graft right ventricular dysfunction. The preoperative assessment of the pulmonary circulation and the calculation of pulmonary resistance are obtained by right heart catheterization after administration of vasodilating agents (Nipride, Dobutamine, Milrinone, NO). It is emphasized that selection of a suitable recipient constitutes the single most important step toward successful transplantation and a long-term survival[7].

Clinical course on the waiting list

Of 71 patients who were listed 12 either refused the proposed procedure or developed complications precluding activation on the list. The majority, 59 patients, were listed but 37 of those (63%) died awaiting a graft, while 22 (37%) were transplanted. The waiting period (mean ± SD) of those transplanted was 166±156 days (range 6-521 days). At regular intervals all patients on the waiting list were

evaluated clinically and checked by right heart catheterization (every three months). An implantable defibrillator was implanted in five patients because of ventricular tachyarrhythmias.

Preoperative inotropic support

In 23 of the 59 (39%) patients on the waiting list, inotropic support was used as a "bridge" to transplantation in addition to the conventional medical regimen. This consisted of the continuous intravenous administration of inotropic drugs with a portable pump in nineteen patients (treatment duration 10±124 months, range 0.1-54 months) or, in four patients, an intraortic balloon pump (I.A.B.P.) in combination with inotropic drugs (duration of I.A.B.P. 34±3 days). Of those 23 patients on home inotropic support 9 (39.1%) died while awaiting a transplant, while thirteen (56.5%) were transplanted. As shown in table 1, of 22 patients transplanted three were supported by I.A.B.P., while thirteen (59%) received continuous home inotropic support as a "bridge". In one patient with end-stage ischemic cardiomyopathy after coronary artery bypass and an LV aneurysmectomy, the continuous inotropic support for 54 months has significantly improved his congestive heart failure and his lifestyle[8]. Mechanical support by means of LVAD, RVAD, biVAD was not employed because these devices were not available in our hospital.

Donor selection

Selection of a suitable donor constitutes the second significant (the other being selection of the appropriate recipient) decision by the transplant team. Usually, donors are younger than 35 years of age in order to preclude coronary disease in the graft. A detailed history to rule out diabetes mellitus, hypertension and C.A.D., is of the utmost importance. Absence of cardiac arrest during or after the accident is desirable as well as avoidance of prolonged hypotension (B.P. < 90mmHg) necessitating administration of excessive amounts of catecholamines. Significant factors in making the selection are donor, sex and distance from the donor hospital, which determines ischemia. In the present study the ischemia time was 186±12min. Recipient dimensions (bodybuild) in relation to those of the donor are of obvious importance. The combination of age, sex, body dimensions and anticipated ischemia time as well as of pulmonary hypertension are of the utmost importance for a successful outcome and can only be mastered after the performance of a substantial number of transplants. It is known that grafts from older donors constitute a risk factor, however grafts from young persons are not always suitable. Graft preservation is effected by means of cold crystalloid cardioplegia.

Operative technique

The technique of orthotopic transplantation has little changed from the time it was described by Lower and Shumway (1960). The operation is performed through a median sternotomy with two venous cannulae inserted in the right atrium while the arterial cannulae is placed in the aorta. After going on bypass the ascending aorta is cross-clamped to avoid dislodgement of any existing clot in the left ventricle. The heart is removed leaving two atrial cuffs *in-situ* containing the caval and pulmonary venous orifices. Suturing of the graft starts from the lateral wall of the left atrium and the stitch is brought circumferentially toward the interatrial septum and the right atrium. Subsequently, the pulmonary arteries and the aorta are sutured using standard techniques.

Immediate postoperative course

The median donor age was 26 years with a range of 15-49 years (18% were over 35 years). The 30-day mortality was 9.1% (2 out of 22 patients) and the cause of death was intraoperative hemorrhage in one patient with two previous heart operations and septic shock due to pseudomonas pneumonia in another with dilated cardiomyopathy. Postoperative complications consisted of pneumonia (5 patients), urinary tract infection (1 patient), cellulitis involving the left jugular vein (1 patient), cardiac tamponade (1 patient), subarachnoid hemorrhage successfully decompressed (1 patient) and humoral rejection (1 patient). Four patients were treated by hemodialysis because of acute tubular necrosis and one was subjected to plasmapheresis. Hospitalization after transplantation was 33±22 days (range 4-85 days), I.C.U. stay was 12.6+7.8 days (range 4-34 days), while time in the Cardiology clinic was 17.9+15 days (range 9-60 days). A triple-drug immunosuppressive protocol consisting of cyclosporin, azathioprine and steroids with induction therapy (A.T.G.)[10,11] was employed. In sixteen patients mycophenolate mofetil (M.M.F.)

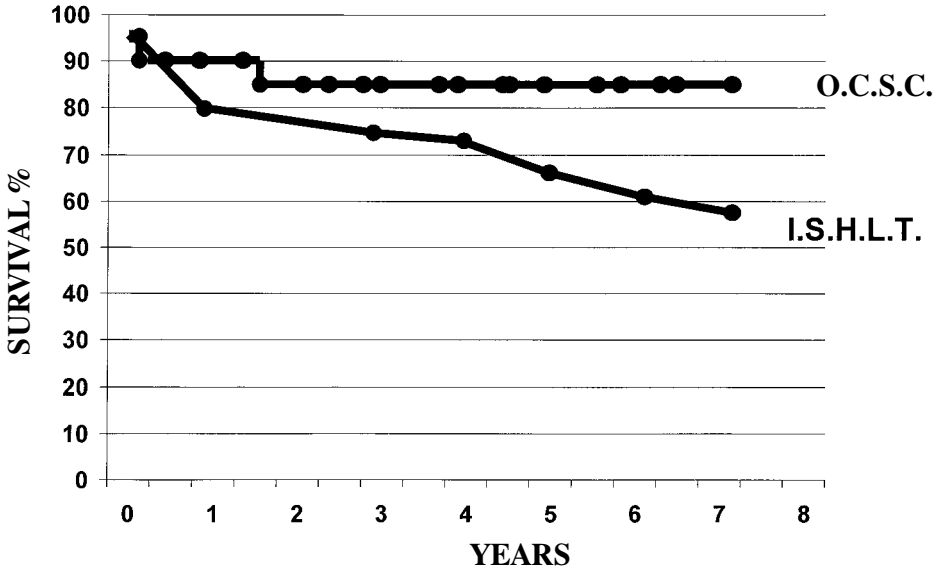

Figure 1. Actuarial survival curve at the Onassis Cardiac Surgery Centre (O.C.S.C.) compared to the international statistics (International Society for Heart and Lung Transplantation).

was used instead of azathioprine. In all patients with a smooth clinical course a serious effort was made to decrease and discontinue steroids in order to avoid the well-known side-effects[12]. Gradually, over the course of the last three years, all patients have been switched to M.M.F. instead of azathioprine. The rest of the medical regime includes antihypertensive and lipid-lowering drugs, as well as agents for the prevention of opportunistic infections. All patients are placed on an early detection of rejection protocol employing frequent endomyocardial biopsies.

Long-term follow up

Of the twenty patients who were discharged after orthotopic heart transplantation one died (5% mortality) because of a lymphoma, 14 months after an otherwise uneventful transplantation. The total mortality, perioperative and long-term, was 13.6% over a follow-up period of 41.7±22.1 months (range 2.5-83 months). Survival at Onassis Cardiac Surgery Centre compares favorably with that reported by the International Society of Heart and Lung Transplantation, as shown in picture 1. During the first year after transplantation all patients are subjected to routine endomyocardial biopsies (initially, once a week) with gradually decreasing frequency. One year after transplantation, all patients are investigated by right and left cardiac catheterization with coronary angiography and an endomyocardial biopsy. The main clinical events during long-term follow-up are listed in table 2. Eleven patients (50%) developed rejection and were successfully treated by optimizing the immunosuppressive regimen. Out of 38 episodes of cellular rejection, 29 (76.3%) were identified in the first six postoperative months. One episode was due to sensitization to DR antigens during pregnancy and early diagnosis facilitated treatment. In the first year after transplantation rejection was identified in 55.5% of the patients, which dropped to 16.7% thereafter. Serious post-operative infections developed in 13 patients (59.1%), especially in the first six months. Among them were C.M.V. infection (7 patients), pneumonia (6 patients), urinary tract infection (2 patients), superficial thrombophlebitis (1 patient), herpes zoster (1 patient) and cellulitis

Table 2. Clinical events of the transplanted patients. Patient number (%).

	0-30 days	1st-6th month	6th-12th month	> 1 year
Patient number	22	20	20	19
Mortality	2 (9.1%)	0	0	1 (5.3%)
Rejection	8 (36.4%)	7 (35%)	1 (5%)	3 (15.8%)
Infections	7 (31.2%)	8 (40%)	1 (5%)	3 (15.8%)
Coronary disease	0	0	0	3 (15.8%)
Neoplasms	0	0	0	1 (5.3%)

along the jugular vein (1 patient). Pulmonary embolism (2 patients), peroneal nerve palsy (1 patient), peripheral neuropathy (1 patient), rhabdomyolysis with acute renal failure due to combined administration of statins and antifungals (1 patient) and cardiac tamponade after biopsy (1 patient), were also encountered. Hip replacement was performed in one patient and a dual-chamber pacemaker was implanted in another patient three years after transplantation, because of AV block (Mobitz 1) with intraventricular conduction disorder. No other important postoperative arrhythmias were noted. Routine coronary angiography identified significant C.A.D. (>50% stenosis of a major coronary artery) in one patient (4.5%), while in two patients there was minor C.A.D. The average interval between transplantation and documentation of C.A.D. was three years (range 2-4 years). Acute myocardial infarction or *de novo* congestive heart failure did not occur. Lymphoma was diagnosed in one patient, fourteen months after surgery and he succumbed to his illness.

Transplant Cost

The total cost from transplant to discharge was calculated at 62,000 ± 23,400 euros (range 46,800-98,000 euros).

Discussion

This clinical study reports the experience of one Transplant Centre in the first seven years of its activity. It is obvious that the long-term results after orthotopic heart transplantation are extremely satisfactory and comparable to those reported by the most experienced Transplant Centres abroad[14, 15].

Lolas et al published their experience with orthotopic heart transplantation in 23 patients, from 1990 to 1994[16]. It was the first organized and detailed analysis concerning the clinical experience of that group which, incidentally, performed the first successful orthotopic heart transplantation in Greece. In comparison to those by Lolas et al, our recipients had similar pulmonary artery pressures but higher pulmonary capillary wedge pressures (26.9 ± 8.7 mmHg vs. 22.9 ± 7.1mmHg) and lower pulmonary resistance (2 ± 1,4 W.U. vs. 2.6 ± 0.8 W.U.) indicative of a more advanced cardiac decompensation, yet of a milder involvement of the pulmonary vasculature. Donors in our clinical experience were somewhat younger (26 years vs. 29.4 years) but ischemia time was longer (almost 3 hours vs. 2.6 hours). Mechanical assistance of the LVAD, RVAD, biVAD modality was not used in either series, while in four of our patients hemodynamic stability was achieved by employing an I.A.B.P. In the aforementioned study the 30-day mortality was 22%, while of the eighteen patients discharged, eight (44%) died during a follow-up of 14.1 ± 11.8 months (total mortality 57% in the first four years of the clinical program). Two patients died because of acute graft dysfunction, six of postoperative infection, while two more succumbed to late graft dysfunction without evidence of cellular rejection. Those results are different from ours, mainly in two points: the development of acute graft dysfunction and the appearance of opportunistic infections. In our experience there was no incident of graft dysfunction despite the need for preoperative inotropic and/or mechanical support in 13 patients (59% of the transplanted patients) This favorable outcome may be attributed to the salutary effect of the inotropic support on pulmonary resistance and justifies the very strict preoperative assessment of pulmonary hypertension by means of pharmacological manipulations. Also we did not experience lethal infections after discharge despite their relatively high incidence during hospitalization (59% of the patients). We attribute this to the standard antibiotic prophylaxis in all patients and to the aggressive treatment of documented infections.

In this initial experience we observed significant mortality (63%) in patients on the active list. Similarly patients on the active list, on home inotropic support, experienced a mortality of 39.1%. It is well known that wold-wide donor shortage constitutes the most significant factor restricting the wide application of heart transplantation. In Greece, in particular, the availability of cardiac donors is the lowest in Europe (1 per million population)[18]. Mobilization and coordination of state agencies along with increased awareness of those involved (medical and nursing staff, administrative personnel) are the *sine qua non* for the wider application of this life-saving procedure for patients with non-reversible congestive heart failure. Rejection and infection are not unusual in this group. The importance of preventive regimens against opportunistic infections (Pneumocystis Carinii, herpes, hepatitis) and of vaccination (against pneumonia, tuberculosis, influenza) should not be underestimated. A small number of patients

developed C.A.D. after the transplant (accelerated graft artherosclerosis)[19]. We have been using a combination of calcium channel blockers and statins in an effort to prevent the development of this serious complication. As expected, C.A.D. developed silently without any symptoms or myocardial infarction.

Heart transplantation in Greece is feasible in a small and strictly selected number of patients with non-reversible congestive heart failure. Long-term results are equal to those of the best Transplant Centres abroad. This success is due to teamwork, meticulous selection of both recipient and donor and the continuous follow-up of these patients for life. The small number of cardiac grafts in our country dictates that only teams with the necessary knowledge, organization and commitment should be allowed in this endeavor.

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