Cardiac Transplantation Under New Legislation for Organ Transplantation in Japan
Report of Two Cases

Soichiro Kitamura, MD; Takeshi Nakatani, MD; Toshikatsu Yagihara, MD;
Yoshikado Sasaki, MD; Junjiro Kobayashi, MD; Ko Bando, MD;
Kenji Minatoya, MD; Akihisa Hanadani, MD; Kazuo Komamura, MD;
Masami Imakita, MD; Chikao Yutani, MD; Masakazu Kuro, MD;
Koji Kimura, MD; Hiroshi Nonogi, MD; Kunio Miyatake, MD

During the past 2 years since new legislation for organ transplantation from brain-dead donors came into effect in Japan, 3 cardiac transplants have been carried out, 2 of which were performed at the National Cardiovascular Center (NCVC). The recipient cases were 46- and 25-year-old male patients who suffered from end-stage dilated cardiomyopathy and had been listed for cardiac transplantation in the Japan Organ Transplantation Network as status 1 candidates. The first patient was supported by the use of a paracorporeal air-driven left ventricular assist device of the NCVC type, and had a moderate degree of renal and hepatic dysfunction at the time of transplantation. Donor hearts were transported from distant hospitals (Tokyo and Miyagi prefecture) and the transportation time was 1 h 33 min and 2 h 4 min, respectively. The operation was performed by the standard technique (Lower-Shumway) in the first patient and by the bicaval anastomosis technique in the second patient. Reperfusion of the transplanted heart was performed retrogradely through the coronary sinus utilizing leukocyte-depleted blood with a gradual increase in temperature. Total ischemic time was 3 h 34 min and 3 h 35 min, respectively. Weaning from the cardiopulmonary bypass was easy and uneventful in each patient. Immunosuppressive therapy was conducted with OKT-3 induction in the first patient because of the coexisting renal dysfunction and with a triple immunosuppressive regimen for both patients. Routine endomyocardial biopsy showed acute rejection of less than grade Ia, and the patients were discharged on the 65th and 46th postoperative day, respectively. At present, both patients are in the NYHA class I state and are ready to return to work. The uneventful recovery seen in these patients shows the advances made in transplant medicine, including the progress and improvement of immunosuppressive therapy, surgical techniques, myocardial protection, and detection and treatment of infection. Further efforts are required to fully establish the cardiac transplantation program in Japan. (Jpn Circ J 2000; 64: 333–339)

Key Words: Brain-dead donor; Cardiac transplantation; Dilated cardiomyopathy; Immunosuppression; Left ventricular assist system

Two years have passed since the new brain death legislation for organ transplantation came into effect in Japan on 16 October 1997. During this period, 4 legally admitted donors appeared, and 3 cardiac, 2 hepatic and 8 renal transplants have been performed. This report describes the 2 cardiac transplants successfully performed at the National Cardiovascular Center (NCVC).

Case Reports

Case 1

The first patient was a 43-year-old male patient whose life had been supported by a left ventricular assist system (LVAS) for 39 days. At age 27, this man was diagnosed as having possible dilated cardiomyopathy (DCM) when he visited a physician presenting the symptom of fatigue easily. Since the age of 29, atrial fibrillation attacks had frequently occurred, resulting in congestive heart failure. At age 35, a coronary-pulmonary fistula was found, for which division surgery was carried out through the first median-sternotomy incision. At age 45, he had an episode of right renal infarction, most probably due to embolism from the heart, but with compensation of the left kidney, overall renal function was kept within the normal limits. He also developed bradycardia associated with atrial fibrillation for which a pacemaker was implanted. In February 1999, he fell into profound heart failure, and intravenous administration of dopamine (DOA), dobutamin (DOB) and milrinone was started. Endomyocardial biopsy (EMB) confirmed the diagnosis of DCM with marked fibrotic changes of the myocardium. Left ventricular function and hemodynamics at the time of entry to the Japan Organ Transplant Network (JOTN) are summarized in Table 1 and Fig.1. The left ventricular cavity was markedly dilated with a reduced ejection fraction (EF) of 11%. The pulmonary capillary wedge pressure (PCWP) increased to 23 mmHg with mild pulmonary hypertension. The cardiac index (CI) was 1.65 L/min-1.m-2. The pulmonary vascular resistance was 1.65 Wood units and the peak oxygen consumption

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Department of Cardiovascular Surgery, Medicine, Radiology, and Pathology, National Cardiovascular Center, Osaka, Japan
Mailing address: Soichiro Kitamura, MD, Department of Cardiovascular Surgery, National Cardiovascular Center, 3-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan
Table 1  Pre- and Postoperative Echocardiographic and Catheterization Data in 2 Cardiac Transplant Patients

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th></th>
<th>Patient 2</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Preop</td>
<td>Postop (12 week)</td>
<td>Postop (25 week)</td>
<td>Preop</td>
</tr>
<tr>
<td>Dd/Ds (mm)</td>
<td>74/68</td>
<td>47/30</td>
<td>50/33</td>
<td>77/71</td>
</tr>
<tr>
<td>EF (%)</td>
<td>11</td>
<td>66</td>
<td>63</td>
<td>23</td>
</tr>
<tr>
<td>MR (grade)</td>
<td>1/4</td>
<td>Trivial</td>
<td>Trivial</td>
<td>2/4</td>
</tr>
<tr>
<td>PA std (mean) (mmHg)</td>
<td>40/22 (29)</td>
<td>20/10 (15)</td>
<td>23/7 (12)</td>
<td>50/30 (39)</td>
</tr>
<tr>
<td>RA (mean) mmHg</td>
<td>(18)</td>
<td>(7)</td>
<td>(5)</td>
<td>(8)</td>
</tr>
<tr>
<td>PCW (mean) mmHg</td>
<td>(23)</td>
<td>(9)</td>
<td>(10)</td>
<td>(28)</td>
</tr>
<tr>
<td>CO(Cl) L/min (L·min⁻¹·m⁻²)</td>
<td>(1.65)</td>
<td>7.21 (4.47)</td>
<td>6.16 (3.83)</td>
<td>(1.81)</td>
</tr>
<tr>
<td>PVR (Wood unit)</td>
<td>1.65</td>
<td>0.83</td>
<td>0.32</td>
<td>(2.78)</td>
</tr>
<tr>
<td>Peak VO₂ (ml·min⁻¹·kg⁻¹)</td>
<td>10.5</td>
<td>12</td>
<td>13.7</td>
<td>–</td>
</tr>
</tbody>
</table>

Dd/Ds, left ventricular diameter, diastolic/systolic; EF, ejection fraction; MR, mitral regurgitation; PA std, pulmonary artery pressure, systolic/diastolic; RA, right atrial pressure; PCW, pulmonary capillary wedge pressure; CO(Cl), cardiac output (cardiac index); PVR, pulmonary vascular resistance; Peak VO₂, peak oxygen consumption.

Fig1.  Patient 1. Pre- (Upper) and postoperative (Lower) echocardiographic findings. (Right panel) M mode view (left ventricle). (Left panel) Short axis view (left ventricle).

was measured as 10.5 ml·min⁻¹·kg⁻¹. On 3 April, his heart failure further worsened and an LVAS of the NCVC type (Toyobo Co) was implanted. This compressed air-driven paracorporeal diaphragmatic pump has 2 mechanical valves incorporated and a 70-ml output chamber. The outlet and inlet cannulae are inserted into the left atrium and the ascending aorta, respectively. The levels of total bilirubin (TB) and serum creatinine (Cr) were elevated to 28 mg/dl and 5 mg/dl, respectively, but slowly recovered following implantation of the LVAS. The patient was soon weaned off catecholamine infusion and started to walk in the ward. He was placed on the waiting list of the JOTN as
a Status I candidate for cardiac transplantation. On 12 May 1999, 39 days after LVAS implant, a brain-dead donor most suitable for this patient became available at the Keio University Hospital. Prior to transplantation, the patient was ambulatory with an LVAS and his renal and hepatic functions were in progressive recovery, but still showed some abnormalities such as Cr 2.1 mg/dl, blood urea nitrogen 60 mg/dl and TB 4.3 mg/dl. Upon receiving information from the JOTN, the final informed consent to undergo a heart transplant operation was obtained. The brain-dead donor was a man in his mid 30s hospitalized for cerebral hemorrhage. A direct lymphocyte cross-match test between the donor and recipient was negative and the donor's heart function was judged to be acceptable by echocardiography and by direct vision during the procurement. The donor's heart was arrested and stored in cold St Thomas solution, then transported to the NCVC by helicopter, charter jet plane and ambulance. Transportation time was 1h 33 min.

The recipient's heart was explanted following dissection of extensive adhesion around the LVAS conduits. The standard technique after the Lower-Shumway original method was used for transplantation. Retrograde reperfusion was using leukocyte-depleted blood was started at the flow rate of 250–300 ml/min, maintaining a coronary sinus pressure of less than 40 mmHg. The temperature of the blood infused was gradually increased from tepid to warm. Total ischemic time was 3h 34 min. The patient was weaned from the cardio-pulmonary bypass of 2h 26 min without difficulty.

Postoperative recovery course was uneventful. Immunosuppressive therapy was begun using methylprednisolone and OKT-3 (muromonab) because of the coexisting renal dysfunction. OKT-3 was used for 10 days at the dose of 5 mg/day. Following stabilization of the clinical state, a triple regimen including Neoral (cyclosporine A), Cellexcept (mycophenolate mofetil) and Prednime (prednisolone) was given. Prednime was started at 20 mg/day and increased to 30 mg/day following completion of OKT-3, which was subsequently reduced to 10 mg/day depending upon the finding of EMB. Cellexcept was given at the dose of 2 g/day and the dose was reduced when the leukocyte count decreased to less than 5000/mm³. The Neoral dose was adjusted to maintain a trough level of around 300 ng/ml. During hospitalization, EMB revealed acute rejection of less than grade Ib, based on the International Society for Heart and Lung Transplantation (ISHLT) criteria. Postoperative hemodynamics and cardiac function were good, as shown in Table 1 and Fig 1. Grade 1/4 mild tricuspid regurgitation was present. He was discharged on the 65th postoperative day as New York Heart Association (NYHA) class 1. Angiography and intravascular ultrasound (IVUS) of the coronary artery of the transplanted heart showed a normal configuration. At 6 months after the surgery, he was in NYHA class I and taking Prednime 7.5 mg/day, Cellexcept 2 mg/day, and Neoral to maintain a trough level of around 300 ng/ml. The human leukocyte antigen (HLA) (A, B, DR) study revealed poor matching (1/6) between the donor and recipient. No apparent symptomatic infection occurred, but the polymerase chain reaction (PCR) and antigenemia examinations and mRNA surveys for cytomegalovirus (CMV) twice yielded positive results. When 2 of these 3 methods gave positive results or an mRNA survey yielded 2+, prophylactic intravenous ganciclovir (3-5 mg/kg) was given. The explanted recipient heart, including both ventricles and one-third of the bilateral atria, weighed 390 g. The left ventricular cavity was markedly dilated with thinned septum and free walls. Fibrosis occupied 26% of the left ventricular myocardium (Fig 2).

Case 2

The second patient who underwent heart transplantation at the NCVC was a 25-year-old man who had been placed on intravenous administration of dobutamine (3 μg - kg⁻¹ · min⁻¹) and milrinone (0.25 μg - kg⁻¹ · min⁻¹) and listed on JOTN as a Status I candidate.

At age 21, he presented with a skip pulse and fainting sensation, then underwent a thorough evaluation including coronary arteriography, left ventriculography and EMB. The diagnosis of DCM was confirmed and β-blocker therapy was prescribed. At age 23, his syncope worsened. Ventricular tachycardia (VT) was detected and amiodarone was prescribed. On 7 August 1998, an automatic cardiac defibrillator was implanted for multifocal VT attacks. Despite the use of β-blocker, angiotensin converting enzyme inhibitor and diuretics, the patient developed pleural effusion, pulmonary congestion, and was admitted emergently to hospital. He was in NYHA class IV and intravenous catecholamine infusion was started. His cardiac function and hemodynamics are shown in Table 1 and Fig 3. Briefly, the left ventricle was markedly dilated to 77 mm in diastole with an EF of 23%. The CI was 1.81 L · min⁻¹ · m⁻² and moderate pulmonary hypertension with a mean pressure of 39 mmHg was present. The pulmonary vascular resistance was 2.78 Wood units.

Several attempts to wean the patient off catecholamine

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failed and on 13 June 1999, 109 days after the initiation of catecholamine treatment, a brain-dead donor became available. The donor was a man in his mid 20s admitted to the Furukawa Municipal Hospital in Miyagi prefecture for brain injury. Organ retrieval was commenced in the afternoon of June 14 and, as in case 1, the donor heart was explanted, stored in cold St Thomas solution and transported to the NCVC by helicopter, jet plane and ambulance. The time required for transportation was 2h and 4 min.

A newer surgical technique, "bicaval anastomosis" was used because this patient had not undergone any previous heart operations and thus, the anatomical identification of the anastomotic areas and postoperative hemostasis was easier than for the patient 1. Reperfusion of the transplanted heart was begun retrogradely through the coronary sinus as was done for the first case. The total ischemic time was 3h 35 min. Anastomosis of the superior vena cava was performed under the beating heart. It was possible to perform direct anastomosis of all parts. Weaning from the cardiopulmonary bypass was easy, although sequential pacing was required for the third grade atrioventricular block, which recovered spontaneously to normal sinus rhythm within 1 day. Otherwise, the postoperative recovery was quite uneventful.

The triple regimen consisting of Neoral, Cellcept and Prednisone was again selected. The patient's postoperative hemodynamics was judged to be excellent (Table 1, Fig 3) and postoperative EMB revealed only an ISHLT grade Ia acute rejection. He was discharged on the 46th postoperative day as NYHA class I. At 3 months after transplantation, a routine EMB demonstrated a grade IIIa rejection (Fig 4), for which steroid pulse therapy using 500 mg methylprednisolone for 3 days was given and successfully ameliorated the rejection to grade Ia (Fig 5). During this episode, no clinical symptoms were observed. Following this treatment, coronary arteriography and an IVUS study both showed a normal coronary artery configuration of the transplanted heart. The patient is now in good health (NYHA class I) preparing to resume his previous work. A retrograde HLA (A, B, DR) study revealed no matching between the donor and recipient.

The explanted recipient's heart weighed 410g. Remarkable dilatation of the left ventricular cavity with thinning of the free wall and septum was evident (Fig 6). Fibrosis occu-
Fig 4. Patient 2. Endomyocardial biopsy of the right ventricle showing acute rejection grade IIIa (International Society of Heart and Lung Transplantation, ISHLT). Multifocal lymphocyte infiltrates and some myocyte damage can be seen (Masson Trichrome, ×40).

Fig 5. Patient 2. Following steroid pulse therapy, acute rejection improved to ISHLT grade Ia. A focal mild infiltrate without myocyte damage can be seen (H&E, ×40).
diesterase III inhibitor and stabilization of the hemodynamics prior to cardiac transplantation by using LVAS with subsequent prevention of multiple organ dysfunction. Two of the 3 patients who underwent cardiac transplantation in Japan had been supported by LVAS. The patient who received a transplant in the Osaka University Hospital had an implantable Novacor LVAS, and the present patient 1 had a paracorporeal Tohoku LVAS of the NCVC type! The number of patients requiring LVAS support as a bridge to the transplant is increasing in Western countries; approximately 60% of patients on LVAS support can be subsequently transplanted and, once transplanted, their 1-year survival rate exceeds 90%. Implantable (intracorporeal) devices, such as the Novacor and TCI heartmate LVAS, are now often used as a bridge to transplantation because they reduce significantly infection and facilitate early rehabilitation, thereby enabling candidates to undergo faster recovery from profound heart failure with multiorgan dysfunction. Furthermore, thromboembolic episodes can be reduced with these devices.

Infection and thromboembolism are the 2 major complications experienced with the extracorporeal LVAS. Because the waiting time of candidates listed for transplantation is much longer in Japan than in other Western countries, we believe that implantable LVAS are needed urgently in order to reduce the incidence of disastrous and sometime fatal complications. Fortunately, cardiac transplantation was performed only 39 days after LVAS implantation in patient 1. No infectious or thromboembolic complications occurred, but renal and hepatic dysfunction remained at the time of transplantation. Following transplantation, recovery was much faster than with an LVAS; the kidney recovered well within 1 week and the liver recovered within 25 days, unaffected by the immunosuppressive agents.

Two surgical techniques were used for the present patients. For patient 1 with an LVAS, the standard Lower-Shumway method was used because of the presence of severe adhesion around the heart with the strong possibility of postoperative hemorrhage? For patient 2, the more recent method of bivacal anastomosis was performed? Aziz et al reported in 1999 that late results are better for the bivacal anastomosis method than for the standard method in terms of the lower incidence of tricuspid regurgitation and pulmonary hypertension, resulting in reduced incidence of right heart failure. The 4-year survival rate is also improved with the newer method. To compensate for the prolonged ischemia of a donor heart transported from a distant hospital, the technique of early reperfusion through the coronary sinus with tepid to warm leukocyte-depleted blood appears to be promising. Retrograde reperfusion at the flow rate of 250–300 ml/min with a coronary sinus pressure of less than 40 mm Hg was successfully used in the 2 patients reported here. It was quite easy to perform and did not disturb the operative view. We will continue to use both bivacal anastomosis and early retrograde reperfusion techniques for cardiac transplantation in our institute.

Only 3 cardiac transplants have been performed during the past 2 years following the establishment of the new law for organ transplantation in Japan, and more than 35 candidates are now on the waiting list of the JOTN. We must continue to make every effort to increase the opportunity to undergo cardiac transplantation for candidates with end-stage heart failure.

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References