Single Lung Transplantation from a Brain-Dead Donor for a Patient With Idiopathic Pulmonary Fibrosis

A Breakthrough After New Legislation in Japan

Two single lung transplants from a single cadaveric donor were successfully conducted at 2 institutions on March 29, 2000, the first such procedure in Japan under newly introduced legislation. Our patient was a 48-year-old woman with idiopathic pulmonary fibrosis who underwent left single-lung transplantation under cardiopulmonary support. The donor lung was preserved in 4°C modified Euro-Collins solution. Total ischemic time was 5 hours and 37 minutes. The postoperative course was uneventful. The patient was discharged on postoperative day 62 with satisfactory respiratory function. (JJTCVS 2001; 49: 398–403)

Key words: single-lung transplantation, pulmonary fibrosis, brain-dead donor

Shinichiro Miyoshi, MD, Masato Minami, MD, Mitsunori Ohta, MD, Meinoshin Okumura, MD, Shin-ichi Takeda, MD, and Hikaru Matsuda, MD.

Since the first successful single lung transplantation (SLT) in a patient with end-stage pulmonary fibrosis by the Toronto Lung Transplant Group[1] in 1983, lung transplantation has evolved into a viable therapeutic option for patients with end-stage parenchymal and vascular pulmonary disease. As of March 2000, 6,514 SLTs and 4,634 double-lung transplants had been registered with the International Society for Heart and Lung Transplantation.[2] In Japan, legislation required to legalize this procedure was enacted in October 1997, and the first heart,[3] liver, and kidney transplants from a brain-dead donor were conducted successfully on February 28, 1999. Lung transplantation, however, was not attempted at that time due to the poor condition of the donor lung. A fifth donor provided organs for 2 SLTs on March 29, 2000, 1 for a patient with lymphangioleiomyomatosis (LAM) at Tohoku University Hospital and 1 for a patient with idiopathic pulmonary fibrosis (IPF) at Osaka University Hospital. We report the left SLT conducted to treat IPF.

From the General Thoracic Surgery, Department of Surgery, Course of Interventional Medicine (E1), Osaka University Graduate School of Medicine, Osaka, Japan.

Received for publication November 21, 2000.
Accepted for publication February 6, 2001.

Address for reprints: Shinichiro Miyoshi, MD, General Thoracic Surgery, Department of Surgery, Course of Interventional Medicine (E1), Osaka University Graduate School of Medicine, 2–2 Yamadaoka, Suita, Osaka 565–0871, Japan.

Case

Patient history. A 48-year-old woman experiencing shortness of breath upon exertion in 1990 was admitted to a hospital reporting exertional dyspnea and edema in her lower extremities in December 1995. A full examination led to a diagnosis of IPF associated with right heart failure. Her condition improved with steroid pulse therapy and diuretics and she was discharged in March 1996 and started on home oxygen therapy. She qualified as a candidate for lung transplantation under our local program on December 6, 1996, then later was recognized by the Japanese Lung Transplantation Committee and registered in the Japan Organ Transplantation Network on August 4, 1998. She required continuing hospitalization beginning in October 1998, due to dyspnea even at rest. On March 28, 2000, a brain-dead donor became available, and our patient was selected as the first-priority recipient. She was subsequently transferred to Osaka University Hospital for lung transplantation. Labora-

Table I. *Laboratory, pulmonary function, and hemodynamic data at patient registration*

Blood Cell Count				
WBC 13090/mm^3	RBC 513 × 10^4/mm^3	Hb 12.0 g/dl	Hct 40.4%	PLT 28.7 × 10^4/mm^3
Chemistry				
Na 139 mEq/l	K 4.7 mEq/l	Cl 98 mEq/l	AST 10 U/l	ALT 5 U/l,
TB 0.3 mg/dl	TP 7.2 g/dl	Alb 3.8 g/dl	Cr 0.5 mg/dl	
Antibodies				
HBsAg –	HCV –	ATLA –	HIV –	CMV +
HSV +	HZV +	EBV +	RS –	Toxo –
Pulmonary Function				
VC 0.82 L (31.2%)		$FEV_{1.0}$ 0.78 L		MVV 33.3 L/min (41.6%)
DLCO 2.71 ml/min·mmHg (13.8%)				TLC 1.54 L (41.1%)
Blood Gas Analysis				
Room air	PH 7.328	PaO2 41.0 mmHg		PaCO2 54.0 mmHg
O_2 2.5L/min	PH 7.324	PaO2 85.0 mmHg		PaCO2 58.7 mmHg
Pulmonary Perfusion Scintigraphy				
Right: Left = 70: 30				
Cardiac Catheterization O_2 2.5 L/min				
HR 90/min	RA 4 mmHg	RV 33/2 mmHg		PA 31/15 (20) mmHg
Ao 146/88 (111) mmHg		CO 3.85 L/min		CI 2.4 L/min/m^2
RI Ventriculography				
First pass		RVEF 32%		LVEF 47%

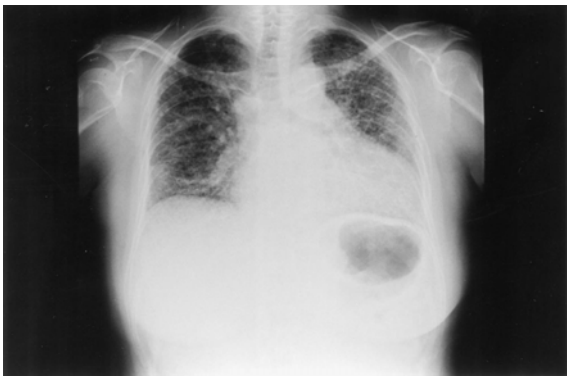

Fig. 1. Preoperative chest X-ray showing cardiomegaly and ground-glass shadows in the lung field.

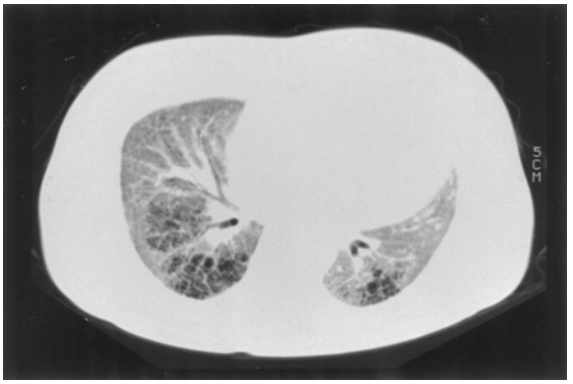

Fig. 2. Preoperative chest CT scan demonstrating honeycomb pattern in the lung field.

tory, pulmonary function, and hemodynamic data at registration are shown in Table I. Pulmonary function tests demonstrated severe restrictive and diffusion disorders. Blood gas analysis also showed severe hypoxemia and hypercapnia. Based on our finding by perfusion scan that the amount of pulmonary perfusion to the left lung was less than that in the right, a left SLT was selected. Hemodynamic data indicated no pulmonary hypertension and cardiac function was maintained relatively well. Chest radiography (Fig. 1) showed cardiomegaly and ground-glass shadows in the lung field on both sides, and chest conputed tomography (CT) (Fig. 2) demonstrated a honeycomb pattern. Alveolar regions could not be sampled by transbronchial lung biopsy. Since no histological diagnosis was obtained, IPF was diagnosed clinically. On admission, the patient was receiving 7 L/min of oxygen and blood gas analysis demonstrated that PaO_2 was 69.7 mmHg and $PaCO_2$ 69.3 mmHg. The woman weighed 50.5 kg and was 152 cm tall. Her medication included 10 mg of prednisolone, 30 mg of azosemide, 200 mg of theophylline, 1 mg of alfacalcidol, 300 mg of ranitidine hydrochloride, and 150 mg of teprenone.

A second informed consent was obtained from her and her family for SLT.

Recipient surgery. The surgical time course is summarized in Table II. The donor was moved to the operating room (OR) of the donor hospital at 10: 29 and the recipient to our OR and general anesthesia

Table II. *Time course of left single-lung transplantation*

Recipient	Donor
10:40 Moved to OR	10:29 Moved to OR
10:53 Anesthesia induced	11:12 Organ procurement started
11:40 Groin incised for PCPS	11:20 Lung assessed macroscopically Blood pressure unstable
	14:00 Donor lung given final assessment
14:14 Skin incised for thoracotomy	14:10 Lung harvest started
14:50 PCPS started	14:59 Harvest completed
	15:29 Departure from donor hospital
	15:55 Departure from Haneda International Airport, Tokyo
	17:00 Arrival at Itami International Airport, Osaka
17:20 Left lung excision started	17:20 Arrival at OR
17:37 Left lung removed	18:03 Donor lung trimming completed
18:11 Bronchus, PV, and PA anastomoses of started	
20:09 Reperfusion started	
20:26 PCPS completed	
22:17 Operation completed	

Fig. 3. Transplanted lung in the left thorax.

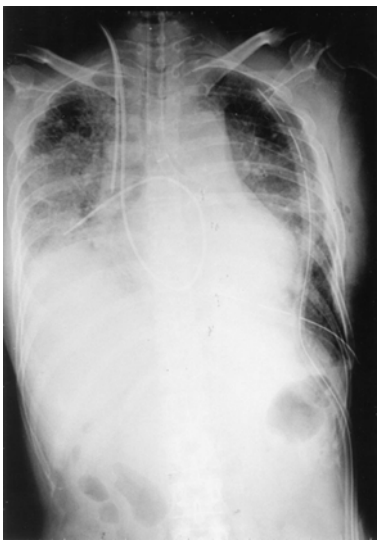

Fig. 4. Chest X-ray in ICU on POD 1.

was induced. After the donor lung was directly evaluated in the operating field, a skin incision was made in the groin of the recipient and the right femoral artery and vein prepared for cannulation for percutaneous cardiopulmonary support (PCPS). The donor lung was finally assessed and harvest started at 14: 10, followed by thoracotomy in the recipient. Due to severe hypoxemia after thoracotomy, cannulation was made to the femoral artery and vein and PCPS started. When the donor lung arrived at the OR, the recipient's left lung was removed and the bronchus, pulmonary vein (PV), and pulmonary artery (PA) anastomosed in order. A telescoping anastomosis using 4–0 PDS was used for the bronchus. Reventilation and reperfusion of the transplanted lung were started at 20: 09 (Fig. 3). The transplanted lung was found to be in excellent condition and the patient was weaned from PCPS in 17 minutes. The chest was closed and the patient transferred to the intensive care unit (ICU) in good condition. Total operation time was 10 hours and 37 minutes, including PCPS of 5 hours and 36 minutes and anastomosis time of 1 hour and 57 minutes. Total ischemic time was 5 hours and 37 minutes. Blood loss was 1250 ml.

Postoperative course. Chest X-ray on the day of surgery (Fig. 4) showed the transplanted lung to be well inflated and free of pulmonary edema due to reperfusion injury. The patient was managed with nitric-oxide inhalation at 16 ppm for 24 hours and

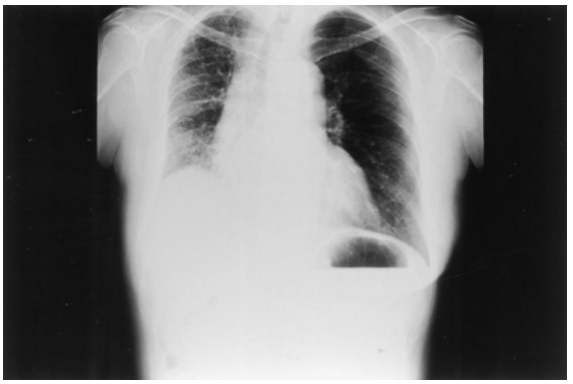

Fig. 5. Chest X-ray on POD 124 showing sufficient inflation of the transplanted lung, with a mediastinal shift to the right and improved cardiomegaly.

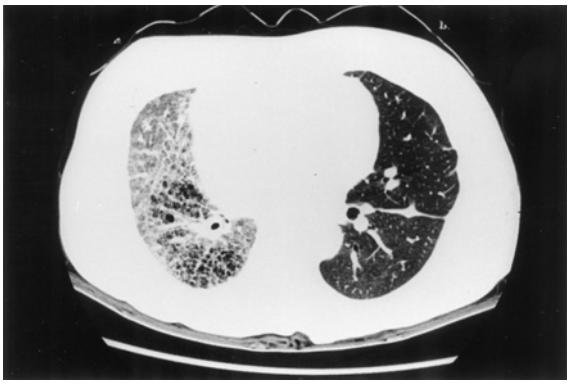

Fig. 6. Chest CT scan on POD 91 showing a normal lung field on the left associated with the honeycomb pattern on the native right lung.

Table III. *Postoperative pulmonary function and 6-minute walk test*

POD	7	16	31	51	61
PaO_2 (mmHg)	54.9	54.1	72.4	84.4	
$PaCO_2$ (mmHg)	48.6	49.6	44.5	40.4	
FVC (L)		0.91 (34.5%)	1.16 (45.1%)		1.51 (58.7%)
FEV1 (L)		0.91	1.10		1.51
Perfusion scan	25:75		30:70		
6-min walk test (m)		250 m	280 m		333 m

m, Meter.

extubated on postoperative day (POD) 3. She left the ICU on POD 6. Her activity improved with vigorous rehabilitation and she was discharged on POD 62. Chest X-ray on POD 124 (Fig. 5) showed the transplanted lung to be sufficiently inflated with a mediastinal shift to the right side and cardiomegaly reduced. Chest CT on POD 91 (Fig. 6) demonstrated a normal left lung field along with the honeycomb pattern on the native right lung. Postoperative functional data (Table III) on arterial blood gas, spirography, and a 6-minute walk test improved steadily. About 70% of pulmonary blood flow shifted to the transplanted left lung. Peak $\dot{V}O_2$ on POD 52 was 484 ml/min (9.86 ml/min/kg).

Immunosuppression. Postoperative immunosuppression was based on a standard triple-drug protocol of cyclosporine, azathioprine, and corticosteroids. Intravenous cyclosporine was given during the first 5 days to maintain a whole blood level of 400–500 ng/ml, followed by oral administration of cyclosporine (Neoral®) at 225 mg × 2 per day. The dose was adjusted to achieve a trough level of 350–400 ng/ml. Prior to surgery, the patient was given 100 mg of azathioprine orally, followed by the same dose until POD 5. Mycophenolate mofetil (Cellcept®) at 1.5 g/day was substituted for azathioprine on POD 6 due to slightly increased total bilirubin of 1.5 mg/dl, after which total bilirubin normalized. On the day of surgery, 1 g of methylprednisolone sodium succinate was given intravenously, followed by 50 mg on POD 1, 2, and 3, and 25 mg on POD 4 and 5. Oral prednisolone at 25 mg/day was started on POD 6. The dose at discharge of Neoral® was 125 mg × 2/day, that of Cellcept® 1.5 g/day, and that of prednisolone 25 mg/day. No acute rejection was observed in a transbronchial lung biopsy at weeks 3 and 6.

Antimicrobial regimens. No significant organisms were found preoperatively in the patient's airway. Sultamicillin tosylate at 1.5 g × 2/day and tobramycin at 60 mg × 3/day were administered intravenously. Although methicillin-sensitive staphylococcus aureus (MSSA) was detected in a sputum culture isolated from the graft bronchus, MSSA was not cultured postoperatively. Since methicillin-resistant staphylococcus aureus (MRSA) was cultured in sputum from the pharynx on POD 2, intravenous trimethoprim-sulfamethoxazole (Bactoramin®) at 1A × 3/day was substituted for antibiotics. Thereafter, oral administration of trimethoprim-sulfamethoxazole (Baktar®) at 4 tab/day was given from POD 6. Inhaled ofloxacin

was added for 1 week. From POD 12, the dose of Baktar® was reduced to 3 times a week for prophylaxis of Pneumocystis carinii. MRSA was not detected after the administration of trimethoprim-sulfamethoxazole. The recipient's serological status of cytomegalovirus (CMV) was positive and that of the donor negative, so CMV hyperimmune globulin was given intravenously for the first 3 days postoperatively. After this treatment, indications for CMV infection treatment were based on weekly monitoring of antigenemia, DNA, and mRNA. Since CMV-DNA was positive in bronchoalveolar lavage fluid on POD 19 and in peripheral blood on POD 26, preemptive therapy of ganciclovir at 5 mg/kg IV daily was conducted for 4 weeks. A 3-day administration of CMV hyperimmune globulin was made twice. CMV-antigenemia, DNA, and mRNA returned to baseline at completion of preemptive therapy.

Discussion

Despite enactment of Japan's organ transplantation law in October 1997, no adequate donor for lung transplantation appeared until March 29, 2000, when 2 single-lung transplants were conducted at 2 institutions from the fifth brain-dead donor. Lungs from the first 4 donors could not be used due to pneumonia. These donations enabled 3 heart, 2 liver, and 8 kidney transplants. The donor aiding our patient provided heart, liver, and 2 kidneys to other recipients.

According to the United Network for Organ Sharing (UNOS) in a 1995 report, only 22% of donors for whom consent was obtained for lung donation in the US actually had a lung recovered, compared to 67% for the heart and 84.5% for the liver.[4] Cadaveric donor lungs are extremely difficult to maintain in good condition on a ventilator.

Cooper and the Toronto Lung Transplant Group initially chose to conduct SLT in patients with end-stage pulmonary fibrosis (PF), similar to our patient, based on the hypothesis that, in end-stage PF patients, the remaining native lung has markedly diminished compliance and increased vascular resistance, so both ventilation and blood flow are preferentially directed to the transplanted lung. These patients ordinarily do not suffer from chronic pulmonary sepsis, and the remaining lung does not pose an infectious risk.[1] Experience with single-lung transplantation for PF has been gratifying and proved this hypothesis.

Chest size matching between the recipient's thoracic volume and the donor's lung volume was initially based on vertical and transverse radiologic dimensions of donor and recipient chests, and matched as closely as possible. This method necessitated that abnormally small donors be selected for PF recipients because the thoracic volume of patients suffering from restrictive pulmonary disease was typically abnormally small.[5] In contrast, we used predicted vital capacity (VC) to compare donors and recipients, and were able to select larger donors for PF patients for left SLT.[5] In the present case, the donor's predicted VC was 142% of the predicted VC of the recipient, and the predicted VC of the graft (left donor lung) was 64% of the recipient. The large transplanted donor lung is considered 1 reason for her excellent postoperative course without reperfusion injury.

We used cold modified Euro-Collins solution for graft preservation. Total ischemic time was 5 hours and 37 minutes. We saw no reperfusion injury in this case. A world-wide survey of 125 centers conducting lung transplantation showed that 77% of centers continue to use Euro-Collins solution, while 13% use University of Wisconsin (UW) solution and 8% Papworth blood-based solution.[6] The maximum ischemic period accepted by centers varies from 4 to 12 hours, with medians of 8 for UW, 7 hours for Euro-Collins, and 6 hours for Papworth solution. Experimental studies have shown that extracellular fluid solution with a low potassium concentration is better for lung preservation than intracellular fluid solution,[7] so extracellular solution use may become more widespread in the near future.

A telescoping technique was used for the bronchial anastomosis, in which wrapping was done with surrounding tissues but without the omentum. Although our patient received 10 mg of prednisolone for 4 years preoperatively, bronchial healing was good without airway complications. It was technically difficult to anastomose the pulmonary vein because of cardiomegaly, while the pulmonary artery presented no problem. Postoperative pulmonary angiography showed no complication at anastomotic sites of the pulmonary artery and vein.

Immunosuppression was started with a standard triple-drug protocol of cyclosporine, azathioprine, and corticosteroids. Neoral®, a new oral microemulsion formulation of cyclosporine, was used because it demonstrated more consistent absorption and predictable pharmacokinetic profile in soft gelatin capsules than current formulation, Sandimmun®.[8] We found that target blood levels of cyclosporine were easily obtained with Neoral®. Cellcept®, a new immunosuppressant,

was substituted for azathioprine. Zuckermann et al. reported that the frequency of acute rejection in lung transplantation was significantly lower in a group with Cellcept® than in a group with azathioprine, although no difference was seen in the rate of infectious disease.[9] Our patient did not experience acute rejection or infectious disease, and is currently enjoying a normal active life.

Lung transplantation in Japan was restarted with a living donor bilateral lobar transplant on October 28, 1998, at Okayama University Hospital.[10] Since then, 5 living- and 3 cadarveric- donor lung transplants have been conducted successfully at 3 institutions Okayama University Hospital, Osaka University Hospital, and Tohoku University Hospital. All 8 recipients are alive and most have already returned to normal active lives. Both living- and cadaveric- donor lung transplantation started at almost the same time in Japan due to a severe donor shortage.

We deeply appreciate the nationwide efforts toward implementing lung transplantation, and are particularly, indebted to the donor and family for their dedication and support. We also wish to acknowledge the vital contributions to this effort made by Osaka University Hospital supporting the transplantation program.

REFERENCES

1. Toronto Lung Transplant Group. Unilateral lung transplantation for pulmonary fibrosis. N Eng J Med 1986; 314: 1140–5.
2. Hosenpud JD, Bennett LE, Keck BM, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: 17 Official Report 2000. J Heart Lung Transplant 2000; 19: 909–31.
3. Matsuda H, Fukushima N, Sawa Y, Nishimura M, Matsumiya G, Shirakura R, et al. First brain dead donor heart transplantation under new legistration in Japan. Jpn J Thorac Cardiovasc Surg 1999; 47: 499–505.
4. Haper AM, Rosendale JD. The UNOS OPTN waiting list and donor registry: 1988–1996. Clinical Transplants. 1996; Chapter 5, 69–90.
5. Miyoshi S, Schaefers HJ, Trulock EP, Yamazaki F, Schreinemakers H, Patterson GA, et al. Donor selection for single and double lung transplantation. Chest 1990; 98: 308–13.
6. Hopkinson DN, Bhabra MS, Hooper TL.: Pulmonary graft preservation: a worldwide survey of current clinical practice. J Heart Lung Transplant 1998; 17: 525–31.
7. Fujimura S, Handa M, Kondo T, Ichinose T, Shiraishi Y, Nakada T. Successful 48-hour simple hypothermic preservation of canine lung transplants, Transplant Proc 1987; 19: 1134–6.
8. Noble S, Markham A. Cyclospolin: a review of the phamacokinetics, properties, clinical efficacy, and tolerability of a microemulsion-based formulation (Neoral). Drugs 1995; 50: 924–41.
9. Zuckermann A, Klepetko W, Birsan T, Taghavi S, Artemiou O, Wisser W, et al. Comparison between mycophenolate mofetil-and azathioprine-based immunosuppression in clinical lung transplantation. J Heart Lung Transplant 1999; 18: 432–40.
10. Date H, Yamamoto H, Yamashita M, Aoe M, Kubo K, Shimizu N. One-year follow-up of the first bilateral living-donor lobar lung transplantation in Japan. Jpn J Thorac Cardiovasc Surg 2000; 48: 648–51.