

Heart-Lung Transplantation in Korea

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Heart-lung transplantation is an effective treatment for patients with various forms of congenital heart disease or pulmonary hypertension. Since the first heart-lung transplantation in 1997,¹ five transplants have been performed in Korea. Three cases were performed in 1997, one in 1998, and the latest one in 2002. The preoperative diagnoses were complex congenital heart disease (CHD) in 2, and CHD with Eisenmenger's syndrome in 3. In this paper, we report five cases of heart-lung transplantation performed in Korea, and include a review of the relevant literature.

Key Words: Heart-lung transplantation in Korea

INTRODUCTION

The brain death law was passed by the Korean parliament in 1999, and the law became effective one year later, with the establishment of KONOS (Korean Network for Organ Sharing). Since then, all activities regarding organ transplantation from a brain-dead donor have been controlled by KONOS, which is located in the National Medical Center in Seoul. Due to the strict nature of the law, the number of organ transplantations performed dropped sharply in 2000. As two of the main purposes of the law are to prohibit the illegal sale of living donor organs, and to promote the fair distribution of organs, it threatens those illegally involved in organ donation with severe punishment. Four years have passed since the law was introduced, and it is perhaps appropriate to briefly describe the current status of thoracic

organ transplantation in Korea, based on KONOS data.

From 1992 to March, 2004, a total of 229 thoracic organ transplantations were performed in Korea, including 215 hearts, 5 heart-lung, and 9 lung transplants. 167 thoracic organ transplants were conducted over the 8 years prior to the introduction of the legislation, and 48 were performed over the 4 years since (Fig. 1 and Table 1).

The first heart-lung transplantation was performed in 1997, on an 11-year-old girl with pulmonary hypertension associated with congenital heart disease.¹ Two more cases have been performed at our center, and two cases at other hospitals; one at the Seoul National University hospital in 1997, and the other at Yongdong Severance hospital, in 2002. All of these cases are briefly described, with a brief discussion, in this paper.

CASE REPORTS

Case 1

An 11 year-old girl with complex congenital heart disease underwent a heart-lung transplantation procedure on April 20, 1997. Her preoperative diagnosis was of pulmonary atresia with intact ventricular septum, right ventricle-dependent coronary circulation, and multiple major aortopulmonary collaterals with pulmonary hypertension.

The donor was a 9-year-old traffic accident victim with the same blood type. The heart-lung block was placed in the chest anterior to the

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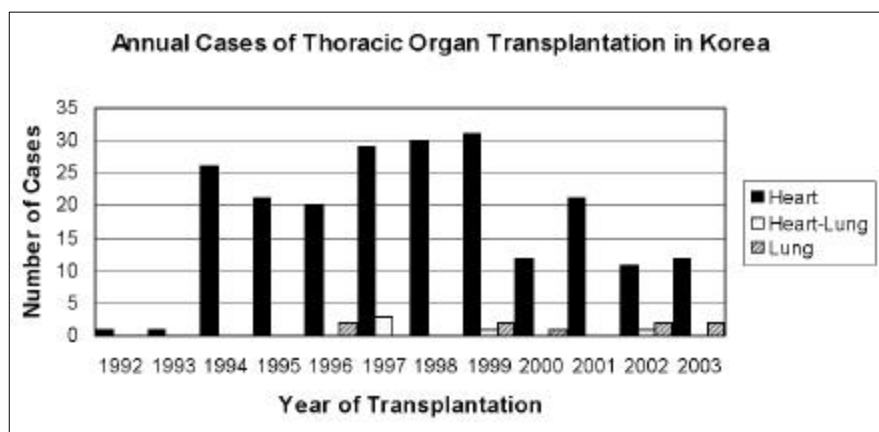


Fig. 1. Annual number of thoracic organ transplants in Korea.

Table 1. Annual Number of Thoracic Organ Transplants in Korea

Year	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	Total
Heart	1	1	26	21	20	29	30	31	12	21	11	12	215
Heart-Lung	0	0	0	0	0	3	0	1	0	0	1	0	5
Lung	0	0	0	0	2	0	0	2	1	0	2	2	9
Total	1	1	26	21	22	32	30	34	13	21	14	14	229

phrenic nerve.² Tracheal anastomosis was completed with a single 4-0 prolene suture (Ethicon, Inc., Johnson and Johnson, Sommerville, NJ, USA) by the continuous over-and-over method. The anastomosis was reinforced by a pericardial flap wrapping. The graft ischemic time was 120 minutes. The patient received initial immunosuppressive agents, including cyclosporine, azathioprine, and intravenous steroid for 2 days, and a 3-day course of rabbit antithymocyte globulin. Oral steroids were withheld for 2 weeks after surgery.

Her postoperative course was uneventful, until the 5th week, at which time she began to experience shortness of breath. Computed tomography and bronchoscopy revealed that her tracheal diameter had narrowed to 4 mm at the anastomosis site, with a deviation to the left. Over the next several weeks, laser ablations of granulation tissue were performed under rigid bronchoscopy, resulting in some symptomatic improvement for 4 weeks. Nevertheless, her respiratory distress ultimately worsened. In order to provide long-term relief for her dyspnea, it was decided to place a stent. She was brought to the cardiac

catheterization room, sedated, and intubated. The stenotic segment was initially dilated with a balloon (Ultrathin balloon, 6 to 12 mm size, Mansfield Co., Boston, MA, USA) to a pressure of between 10 and 14 atmospheres. A Palmaz stent (8 mm × 30 mm, Johnson & Johnson Interventional Systems Co., Warren, NJ, USA) was then delivered into the dilated lesion and inflated at high pressure (Fig. 2). After this procedure, her shortness of breath disappeared, and she was extubated on the same day. One month later, repeat ballooning was attempted to further increase the stent dimension, in an attempt to fix the lower stent end to the tracheal wall, but this procedure met with only limited success.

The patient had been doing well for 9 months after stent placement, when she suddenly developed shortness of breath and a mild fever. An endoscopic examination revealed an intraluminally-growing fungal mass. Surgical removal and repair of the trachea were considered, coupled with the administration of antifungal agents. However, the patient's condition deteriorated rapidly and she died the day after admission.

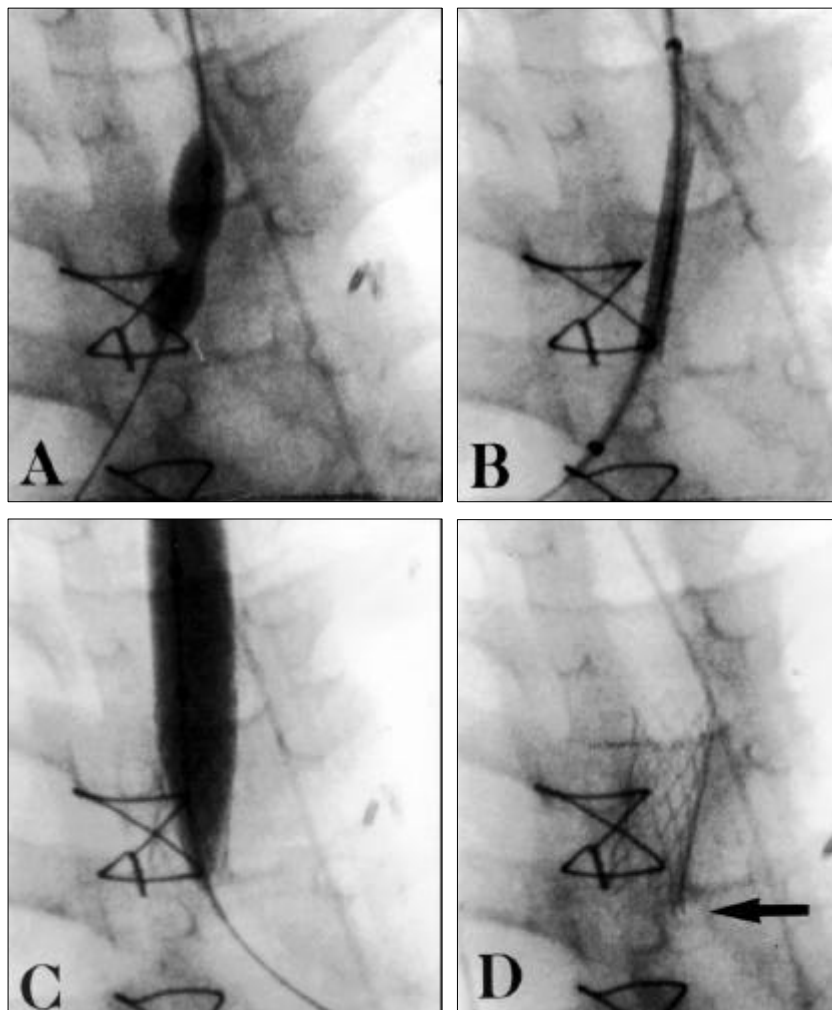


Fig. 2. Fluoroscopic view of stent placement on the 71st postoperative day. The stenotic trachea was first dilated by a balloon (A) and an expandable metallic stent (8 × 30 mm, Palmaz, Johnson and Johnson) was delivered by an Ultrathin balloon (6 to 12 mm size, Mansfield Co., Boston) (B) and inflated at high pressure (C). Note the distal tip of the stent is floating free after the stent placement, which later became a nidus for *Candida* infection (D, arrow).

Case 2

The following case involved Dr. Rho and his team at Seoul National University in 1997.³ The patient was a 32-year-old female with Eisenmenger's syndrome, secondary to patent ductus arteriosus. She had suffered from congestive heart failure since June 1996, and had been repeatedly treated with intravenous inotropics in the intensive care unit. Preoperative echocardiography revealed a patent ductus arteriosus with a right to left shunt, severe regurgitation in the tricuspid valve, and an estimated right ventricular systolic pressure of 100 mmHg. The brain-dead donor was

an 18 year-old male with head trauma resulting from a traffic accident occurring 3 days previous to death. Heart-lung block procurement was performed at another general hospital, then transported to Seoul National University Hospital by ambulance. Total ischemic time of the transplanted heart and lung were 249 and 270 minutes, respectively. Immunosuppressive therapy commenced preoperatively, and consisted of cyclosporine and azathioprine. Corticosteroids were not administered until 3 weeks postoperatively, in order to avoid infection and delayed healing at the tracheal anastomotic site. The patient was discharged on the 31st postoperative day, and has

been doing well until now. Follow-up bronchoscopy, performed 2 weeks and 4 months after surgery, revealed no evidence of cellular rejection.³

Case 3

This case was performed 8 months after the first heart-lung transplantation case at our center, on December 25, 1997. A 12-year-old boy who had been diagnosed as having complex congenital heart disease with corrected TGA, pulmonary atresia, VSD, multiple major aortopulmonary collateral arteries, and dextrocardia, was referred to our center for heart-lung transplantation. The donor was a 9-year-old female with a brain tumor. The heart-lung block was prepared at another university hospital in Busan, and transported by commercial airline and helicopter to our center. The graft ischemic time was 286 minutes, including 120- minutes of transportation time. The transplantation technique details were identical to those of case 1. Postoperatively, the patient exhibited persistent mucopurulent expectoration, an examination of which yielded *Pseudomonas aeruginosa*, resistant to all antibiotics except Imipenem. The origin of the pseudomonas infection was surmised to be the donor's lungs, which, upon culturing, yielded the same organism. The patient had been treated for pseudomonas infection for two years, which had included trials of various antibiotics, namely, Imipenem, Ceftazidime, Ciprofloxacin, Tienam, and aminoglycosides. However, the sputum culture continued to show growth of the same organism. During treatment for lung infections, the patient experienced tracheal anastomotic stenosis, which was treated by balloon dilatation. On his 49th postoperative day, the patient's mother wanted to take him to the hospital nearer to the family home, and he was transferred to a hospital in Seoul. Immunosuppression was performed with cyclosporine, mycophenolate mofetil, and intermittent corticosteroids. Within 1 year, the steroid treatments was tapered off and stopped in order to minimize the risk of lung infection. *Pseudomonas aeruginosa* treatment continued at the hospital, but the patient died 18 months after the operation.

Case 4

A 38-year-old male patient with VSD and Eisenmenger's syndrome was referred to our center for heart-lung transplantation. Cardiac catheterization evidenced VSD with fixed severe pulmonary hypertension. His pulmonary artery pressure was 105/60 mmHg, whereas his systemic pressure was 110/70 mmHg. The patient's calculated pulmonary artery resistance was 12.35 wood units, and proved unresponsive to pulmonary vasodilators, whereas his indexed systemic resistance was 35.72 wood units. After 10 months on the waiting list, he underwent heart-lung transplantation with the same technique described for cases 1 and 3. The donor was a 40-year-old male who had died of traumatic cerebral stroke. The graft ischemic time was 210 minutes. The transplant patient's postoperative course was initially uneventful, and he was able to be extubated on his first operative day. On his 10th postoperative day, he manifested a spike of fever suggestive of pulmonary infectious complications. Bronchoscopy performed on the 12th day revealed edematous and bloody mucosa surrounding the tracheal anastomotic site. A bronchoscopic culture of the lesion yielded *Escherichia coli*, which proved to be sensitive to both Bactrim and Amikin. Sensitive antibiotics were continuously administered intravenously, resulting in some improvement of the patient's dyspnea. However, repeat bronchoscopy, performed on the 18th postoperative day, revealed partial dehiscence of the tracheal anastomosis, coupled with inflamed adjacent mucosa. Thoracotomy and reapproximation of the trachea was performed, but the patient died two months after the operation.

Case 5

This case involved Dr. Paik at Yongdong Severance Hospital, on November 29, 2002.⁴ The patient was a 41-years-old male, who had been diagnosed with Eisenmenger's syndrome, due to patent ductus arteriosus and VSD. His relevant pressures were as follows: aorta 130/80, mean 100 mmHg, pulmonary artery 130/80, mean 109 mmHg, right ventricle 130/20 mmHg, and right atrium, mean 20 mmHg. The donor was a 24 years-old male

who had been diagnosed as brain dead as the result of a subdural hematoma. Ligation of the patent ductus arteriosus was performed under cardiopulmonary bypass, followed by heart-lung transplantation. The patient was extubated on postoperative day one, transferred to a general ward on day 3, and finally discharged on postoperative day 33. The patient was in stable condition until the 22nd postoperative day, at which time he complained of acute abdominal pain. A simple abdominal X-ray revealed free air in the patient's abdominal cavity. He underwent emergency laparotomy and wedge resection of perforated stomach. The postoperative course was uneventful, and he was discharged on 32nd postoperative day. However, the patient died 7 months later, from a CMV (cytomegalovirus) infection.

DISCUSSION

Since the first successful clinical heart-lung transplantation by Dr. Reitz of Stanford, California in 1981, heart-lung transplantation has become a standard therapy for patients with primary pulmonary hypertension and Eisenmenger's syndrome with congenital heart disease.⁵ Moreover, considerable advances have been made from the time of the procedure's inception, in terms of both morbidity and mortality. However, the number of centers reporting heart-lung and lung transplants has gradually declined since the mid-1990s. Annual heart-lung transplantation activity has decreased by more than 50% since 1995, and annual number of procedures has plummeted from more than 200 in 1995, to less than 70 in 2001. This decline could be attributed to several factors. One of the main factors is that lung transplantation has, at least partially, supplanted heart-lung transplantation for some indications, most notably, cystic fibrosis, chronic obstructive pulmonary disease, and primary pulmonary hypertension. Increasing competition for donor hearts for cardiac transplantation has probably also contributed to this trend,⁶ and it is likely that the higher mortality and morbidity associated with heart-lung transplantation, as opposed to other forms of thoracic organ transplantation, is

also a factor.

In Korea, the need for brain-death legislation drew public attention in 1988, when Dr. ST Kim of Seoul National University performed the first liver transplantation from a brain-dead patient, a 14-year-old female with Wilson's disease. The case resulted in an official announcement to the effect that organs from a brain-dead patient had been used, which resulted in heated debate, eventually paving the way for the introduction of brain-death legislation in Korea in 1999.

In Japan, a similar brain-death law had been introduced two years earlier, in 1997. The first heart transplantation was performed by Dr. Wada of Sapporo Medical University, in 1968. However, public opinion was unfavorable, and the doctor was even accused of murder. At that time there was much argument as to whether the donor was really dead. It is no wonder that the Japanese were so reluctant to accept legislation on the topic, which was finally enacted on October 16, 1997. The Japanese Organ Transplantation Network (JOTNW) was subsequently established, some 2 years earlier than in Korea. However, it took another 2 years after the introduction of the brain death legislation for the second heart transplantation to be attempted, which was undertaken successfully in Japan in February, 1999.

In Korea, the annual number of thoracic organ transplants was appeared to be either slightly increasing, or at least remaining stable, before the establishment of the brain-death law. However, after the establishment of KONOS, the number declined sharply, and has since stabilized between 10 - 20 per year (Table 1). An active donor action program is being planned by the steering committee of KONOS. In 2003, the total number of brain-death donors in Korea was 68, and the average number of organ donations from brain death cases per 1,000,000 in the Korean population is 1.6, which is far behind the 10 - 20 found in Western countries. Every effort is currently being made to improve the organ shortage problem. KONOS has set criteria which classify each candidate according to urgency, blood group, history of organ donation, region, etc. If a donor is available, these criteria are used to identify candidate recipients. This system has operated well for four years, and has elicited excellent response.

One of the main risk factors affecting the high postoperative mortality and morbidity associated with heart-lung transplantation is grafted lung infection. According to the data registry of the International Society of Heart and Lung Transplantation (ISHLT),⁶ technical complications, graft failure, and non-CMV infections account for approximately 80% of deaths occurring during the first 30 days. Non-CMV infections are the leading cause of death for the remainder of the 1st year, and remain the leading factor until the 3rd year after operation. Direct communication between the transplanted organ and the environment, the impairment of local host defenses (e.g. mucociliary clearance and cough reflex), the disruption of lymphatic drainage, ischemic airway injury, altered alveolar phagocytic function, and a greater overall requirement for immunosuppression, all contribute materially to the unique susceptibility to various infections observed in lung and heart-lung transplant recipients.⁷

We lost all 3 of our cases due to grafted lung infection, either at the anastomotic site (cases 1 and 4) or in the lung parenchyma (case 3). The infection came directly from the donor in two cases (cases 3 and 4), as indicated by the isolation of identical organisms in donors.

We lost case 1 due to a *Candida albicans* infection in a stent inserted to treat a tracheal anastomotic site. Although the incidence of anastomotic tracheal stenosis after heart lung transplantation is becoming less common nowadays, it continues to be a major postoperative morbidity and mortality threat.⁸ The absence of a systemic vascular supply to the anastomotic trachea plays a major role in the initiation of airway-related complications. The gross pathology of lesions vary, ranging from mucosal web formation to frank necrosis, involvint complete obstruction or dehiscence.⁹ Numerous attempts have been made to solve these problems, including excision via endoscopic cautery, or laser, and balloon dilatation. The balloon expandable Palmaz stent (Johnson and Johnson Interventional Systems Co., Warren, NJ) is constructed of stainless steel in the form of tubular mesh, and was designed specifically for vascular stenosis.¹⁰ More recently, the indications for its use have expanded toward both benign and malignant tracheobronchial stenotic lesions. These

stents are available in many internal diameters and lengths. Prior to expansion, the correct choice of length and maximum stent diameter are critical, as it is practically impossible to remove or reposition a stent once it is deployed. In case 1, ballooning and laser ablation were attempted before stenting, but did not result in long-term relief. However, immediate symptom relief did occur, followed by recurrence of respiratory distress after several weeks. The free floating of the distal end of the stent was caused, in part, by deviation of the stenotic trachea to the left, which was exacerbated by the small size of the stent. It was also discovered that the distal tip of the stent went too deep from the narrowest point (Fig. 1D). This floating of the distal end of the stent was believed to act as a nidus for the aforementioned fatal *Candida albicans* infection.

In cases 3 and 4, however, the infecting organisms were discovered to have come directly from the donors. Cultures from both donor and recipient yielded identical organisms. In case 3, the organism isolated was *Pseudomonas aeruginosa*, one of the most common pathogens in immunosuppressed patients.¹¹ This patient had been placed on a variety of intravenous and aerosol administered antibiotics. However, the infection could not be completely eradicated. In case 4, the operation itself was successful, except for the anastomotic site infection caused by *Escherichia coli* (*E. coli*). A tracheal aspirate culture yielded *E. coli*, identical to that detected in the donor tracheal aspirates. We must confess that it was our mistake not to wait until the results of the tracheal culture were available. However, we could not justify spending one or two days waiting for culture results, as organ teams had already been assembled.

Although the number of total thoracic organ transplantations being performed is obviously limited, heart transplantation is a well established procedure. However, lung and heart-lung transplantation, in Korea, remains in its infancy.

REFERENCES

1. Park K-Y, Kim J-E, Park C-H, Kim SI, Kim J-C, Hyun S-Y, et al. The First Successful Heart-Lung Transplan-

- tation in Korea. Korean J Thorac Cardiovasc Surg 1998; 31:610-4.
2. Lick SD, Copeland JG, Rosado LJ, Arabia FA, Sethi GK, et al. Simplified Technique of Heart-Lung Transplantation. Ann Thorac Surg 1995;59:1592-3.
 3. Rho JR, Huh J-H, Oh SS, Kim YT, Lee JR, Kim K-B, et al. A Case Report of Heart-Lung Transplantation. Korean J Thorac Cardiovasc Surg 1998;31:1004-8.
 4. Paik HC, Hong YS, Kim DH, Ham SJ, Lee KJ, Lee DY, et al. Heart-Lung Transplantation in a Patient with VSD, PDA and Eisenmenger's Syndrome. Korean J Thorac Cardiovasc Surg 2003;036:418-21.
 5. Reitz BA, Wallwork JL, Hunt SA, Pennock JL, Billingham ME, Oyer PE, et al. Heart-lung transplantation. Successful therapy for patients with pulmonary vascular disease. N Engl J Med 1982;306:557-64.
 6. Trulock EP, Edwards LB, Taylor DO, Boucek MM, Mohacsi PJ, Keck BM, et al. The Registry of the International Society for Heart and Lung Transplantation: Twentieth Official adult lung and heart-lung transplant report-2003. J Heart Lung Transplant 2003;22:625-35.
 7. Nina Singh, Husain S. Aspergillus Infections After Lung Transplantation: Clinical Differences in Type of Transplant and Implications for Management. J Heart Lung Transplant 2003;22:258-66.
 8. Colquhoun IW, Gascoigne AD, Au J, Corris PA, Hilton CJ, Dark JH. Airway Complications after Pulmonary Transplantation. Ann Thorac Surg 1994;57:141.
 9. Higgins R, McNeil K, Dennis C, Parry A, Large S, Nashef S, et al. Wells, Christopher Flower, and John Wallwork. Airway Stenoses after Lung Transplantation: Management with Expanding Metal Stents. J Heart Lung Transplant 1994;13:774-8.
 10. Filler RM, Forte V, Fraga JC, Matute J. The Use of Expandable Metallic Airway Stents for Tracheobronchial Obstruction in Children. J Pediatr Surg 1995;30:1050-6.
 11. Flume PA, Egan TM, Paradowski LJ, Detterbeck FC, Thompson JT, Yankaskas JR. Infectious complications of lung transplantation. Impact of cystic fibrosis. Am J Respir Crit Med 1994;149:1601-7.