Fig. 1 Annual number of candidates for brain-dead-donor lung transplantation newly registered at the Japan Organ Transplantation Network and active on the waiting list. Both newly registered patients (*blue column*) and patients active on the waiting list at the end of the year (*red line*) are increasing

Fig. 2 Number of lung transplantations performed at each lung transplant center in Japan. *LTx* lung transplantation, *Tx* transplantation

world; more than 40,000 cases of lung transplantation have been reported in the registry of the International Society for Heart and Lung Transplantation [1]. Lung transplantation was initiated in Japan in 1998 by the performance of a living-donor lobar lung transplantation at Okayama University [2]. The Japanese Organ Transplant Law took effect in 1997, and the first lung transplantations from a brain-dead donor were conducted in 2000 at Tohoku University and Osaka University [3]. In July 2010, the revised Japanese Organ Transplant Law allowed the procurement of organs from a brain-dead donor if the person did not oppose the procurement of his or her organs while he or she was alive and if his or her family consents to the organ donation. This revised law resulted in an increase in the number of organ donations from brain-dead donors in Japan [4]. Nevertheless, the number of potential lung transplant candidates registered at the Japan Organ Transplantation Network has been increasing as well, resulting in a severe donor shortage.

Eight transplant centers (Tohoku, Dokkyo, Chiba, Kyoto, Osaka, Okayama, Fukuoka, and Nagasaki Universities) are currently authorized to perform lung transplantation in Japan. By the end of 2013, a total of 344 lung transplantations (145 living-donor and 199 brain-dead-donor lung transplantations) had been performed. The clinical data of these 344 lung recipients have been registered and systematically accumulated by the Japanese Society of Lung and Heart–Lung Transplantation. Data regarding recipients on the waiting list and offers from brain-dead donors were collected from the Japan Organ Transplant Network. This report
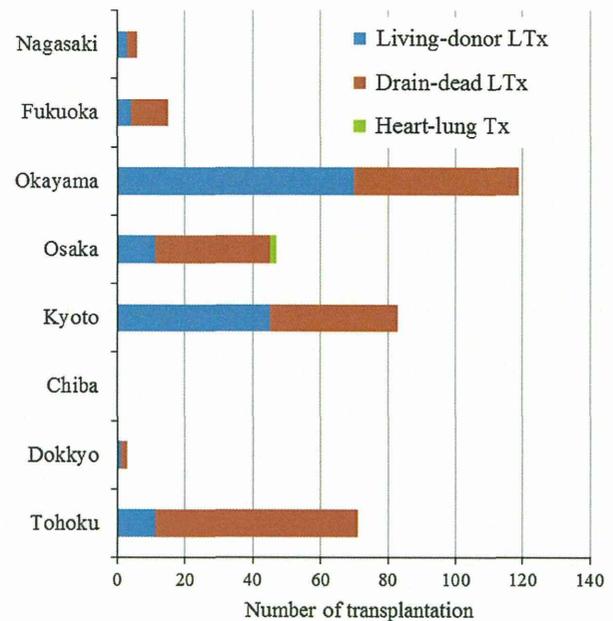
summarizes the current status of lung transplantation in Japan.

Lung transplant waiting list

The number of lung transplant candidates newly registered at the Japan Organ Transplantation Network has generally been increasing. Accordingly, the number of patients on the waiting list is also increasing (Fig. 1). After the revised Japanese Organ Transplant Law took effect in July 2010, the number of newly registered patients almost doubled, reaching nearly 100 in 2011 and exceeding 100 for the first time in 2013. A total of 788 candidates had been registered by the end of 2013. During the last 17 years, 199 patients underwent lung transplantation using brain-dead-donor lungs, and 302 patients died while waiting for lung transplantation. As of the end of December 2013, there were 237 patients on the waiting list (188 patients were active on the list).

Number of lung transplantations

Seven transplant centers (Tohoku, Dokkyo, Kyoto, Osaka, Okayama, Fukuoka, and Nagasaki Universities) had previously been authorized to perform lung

transplantation in Japan; Chiba University was added to this list in 2013. Among these centers, Tohoku and Osaka Universities are approved for combined heart–lung transplantation. The numbers of lung transplants performed at these eight centers are shown in Fig. 2. The cumulative number of lung transplants is 344, including 145 living-donor lung transplants, and 199 brain-dead-donor lung transplants (93 bilateral lung, 104 single lung, and 2 heart–lung transplants). The number of transplants per year and the ratio of brain-dead-donor transplants have increased (Fig. 3).

In total, 251 brain-dead donations were offered, and 164 were accepted for transplantation; 294 of 502 (251 × 2) lungs were used (1.17 lungs per donor). Thus, 65.3 % of donors (per donor) and 58.6 % of lungs (per lung) were actually used for transplantation. The annual numbers of

brain-dead donations offered and accepted for lung transplantation are shown in Fig. 4.

Indications

The primary indications for unilateral and bilateral brain-dead-donor lung transplantation and living-donor lung transplantation are shown in Fig. 5. The indications for the two cases of heart–lung transplantation were Eisenmenger syndrome and pulmonary hypertension complicated by restrictive cardiomyopathy. The age distribution of the recipients is shown in Fig. 6. The mean ages of the recipients of brain-dead-donor and living-donor lung transplantation were 40.0 (13–61) and 31.7 (3–64) years, respectively.

Survival

The survival of lung transplant recipients registered with the Japanese Society for Lung and Heart–Lung Transplantation is shown in Fig. 7. The follow-up data of the first lung transplantation of retransplant cases were censored on the day of retransplantation. The benchmark overall survival rates were 95.5 % at 1 month, 92.2 % at 3 months, 86.2 % at 1 year, 79.6 % at 3 years, and 73.7 % at 5 years. The survival curves for brain-dead-donor and living-donor lung transplantation were similar (Fig. 7a). The early mortality rates following bilateral brain-dead-donor and single living-donor lung transplantation were higher than those following single brain-dead-donor and bilateral living-donor lung transplantation (Fig. 7b). The
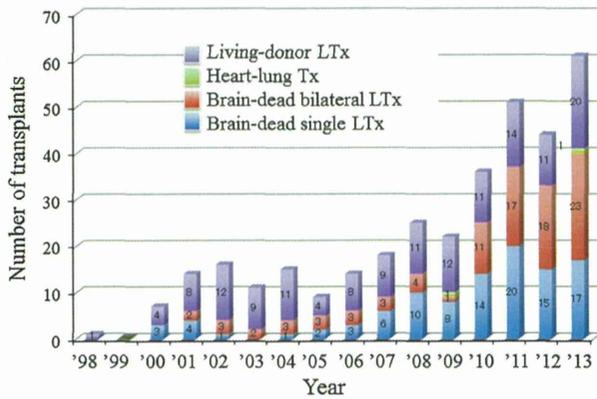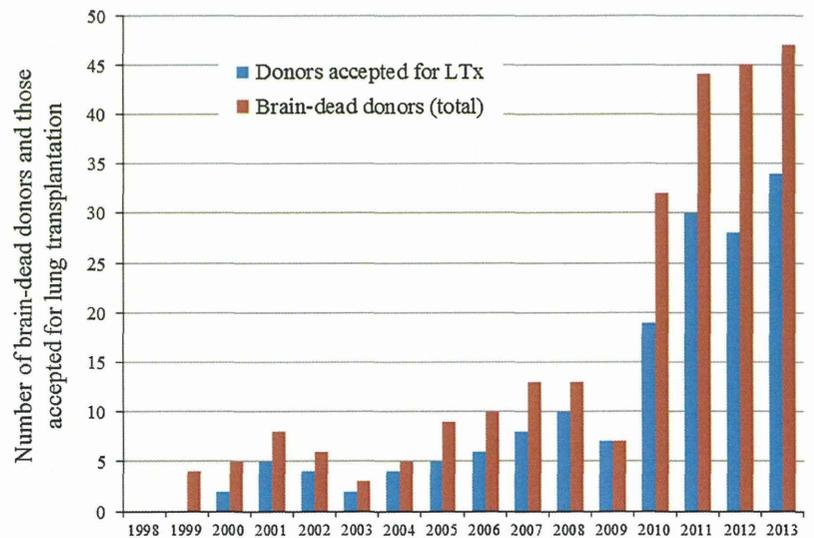

Fig. 3 Annual numbers of lung transplantations performed during 1998–2013. *LTx* lung transplantation, *Tx* transplantation

Fig. 4 Numbers of brain-dead donors and donors accepted for lung transplantation. *LTx* lung transplantation

Fig. 5 Indications for brain-dead-donor and living-donor lung transplantation. *LTx* lung transplantation, *LAM* lymphangioleiomyomatosis, *IIP* idiopathic interstitial pneumonia, *COPD* chronic obstructive pulmonary disease, *IP* interstitial pneumonia, *BO* bronchiolitis obliterans, *PAH* pulmonary arterial hypertension, *BE* bronchiectasis, *DPB* diffuse panbronchiolitis, *CF* cystic fibrosis, *CTEPH* chronic thromboembolic pulmonary hypertension
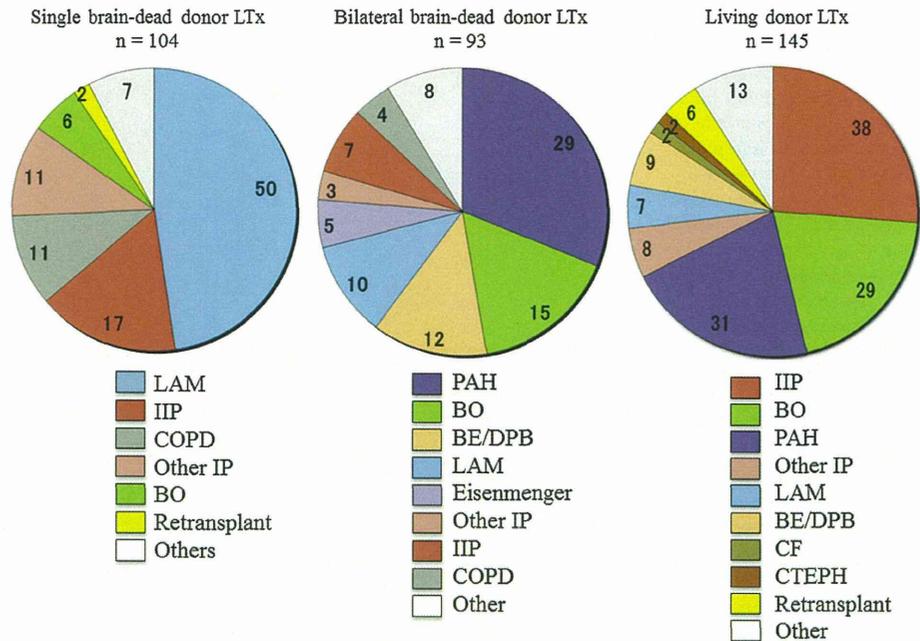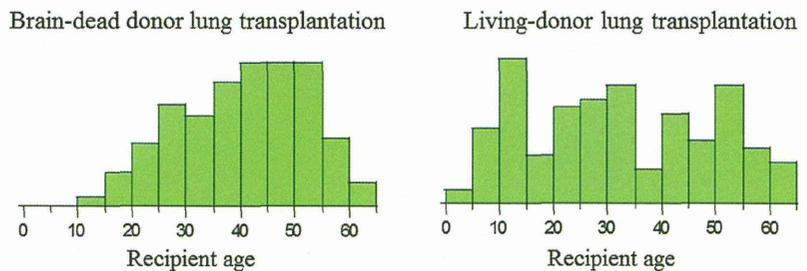
Fig. 6 Age distribution of lung transplant recipients in Japan

survival of lung transplant recipients stratified by the original diagnosis is shown in Fig. 7c.

Functional status

An excellent post-transplant functional status was observed in lung transplant recipients. More than 80 % of the brain-dead-donor and living-donor lung recipients who survived had a Hugh–Jones classification of I or II (Fig. 8). Approximately 80 and 70 % of recipients in the living-donor and brain-dead-donor lung transplant groups, respectively, returned to normal life (i.e., full- or part-time work, work at home, or school) (Fig. 9).
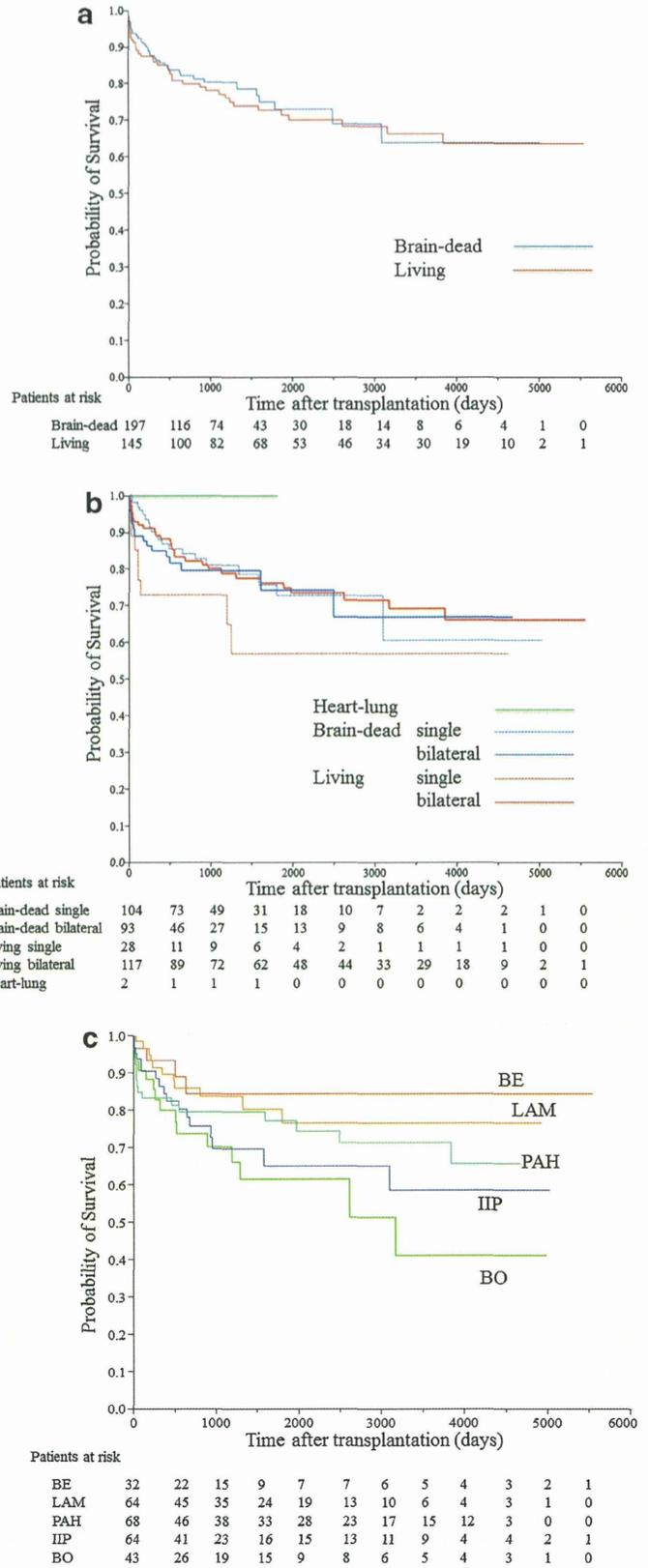
Causes of death

A total of 76 of 344 recipients died for a variety of reasons (Fig. 10). Infection was a significant cause of death

throughout the observation period. Graft failure was the primary cause of death in the early post-transplant period, while chronic rejection or chronic lung allograft dysfunction including bronchiolitis obliterans syndrome was a predominant cause of death after 1 year. Post-transplant lymphoproliferative disorder and recurrence of the original hematologic malignancy in recipients of hematopoietic stem cell transplantation were the two leading causes of post-lung transplant mortality associated with malignancy.

Pediatric lung transplantation

Forty-two lung transplants (38 living-donor and 4 brain-dead-donor lung transplants) were performed in pediatric recipients (age of <18 years). The distribution of recipients by age is shown in Fig. 4. Living-donor lung transplantations were performed in 2 1- to 5-year-old children, 16 6- to 10-year-old children, and 24 11- to 17-year-old children. The ages of the four brain-dead-donor lung recipients were

Fig. 7 Survival of lung transplant recipients. **a** Survival of patients sorted by brain-dead-donor and living-donor lung transplantation. **b** Survival of patients sorted by transplant procedures. **c** Survival of patients sorted by the original diagnosis. *BE* bronchiectasis, *LAM* lymphangioleiomyomatosis, *PAH* pulmonary arterial hypertension, *IIP* idiopathic interstitial pneumonia, *BO* bronchiolitis obliterans. Note that diffuse panbronchiolitis and cystic fibrosis are also included in BE; BO includes idiopathic BO and BO secondary to specific causes including hematopoietic stem cell transplantation. Cases of lung retransplantation were excluded

Patients at risk											
Brain-dead	197	116	74	43	30	18	14	8	6	4	1	0
Living	145	100	82	68	53	46	34	30	19	10	2	1

Patients at risk											
Brain-dead single	104	73	49	31	18	10	7	2	2	2	1	0
Brain-dead bilateral	93	46	27	15	13	9	8	6	4	1	0	0
Living single	28	11	9	6	4	2	1	1	1	1	0	0
Living bilateral	117	89	72	62	48	44	33	29	18	9	2	1
Heart-lung	2	1	1	1	0	0	0	0	0	0	0	0

Patients at risk											
BE	32	22	15	9	7	7	6	5	4	3	2	1
LAM	64	45	35	24	19	13	10	6	4	3	1	0
PAH	68	46	38	33	28	23	17	15	12	3	0	0
IIP	64	41	23	16	15	13	11	9	4	4	2	1
BO	43	26	19	15	9	8	6	5	4	3	1	0

13, 14, 17, and 17 years. The Kaplan–Meier survival curves estimated for the pediatric and adult lung transplantations are shown in Fig. 11. Although the number of pediatric patients was small, pediatric lung transplant recipients showed a trend toward better long-term survival than adult patients.

Discussion and conclusion

In 2011, just after the revised Japanese Organ Transplant Law took effect, the number of organ donations by brain-dead donors significantly increased. However, the number of brain-dead donors has remained almost unchanged for

the last 3 years, while the number of lung transplant candidates registered at the Japan Organ Transplantation Network has increased. Thus, the organ shortage in Japan is still so severe that many patients registered at the Japan Organ Transplantation Network die without the opportunity to receive lung transplantation.

Interestingly, the number of living-donor lung transplantations increased last year. This may suggest improved recognition of lung transplantation as a life-saving option for patients with terminal respiratory disorders by the society and particularly by patients, family members, and physicians. It is probable that the increase in the number of potential lung transplant candidates resulted in an increase in the number of suitable candidates for lung transplantation from living donors.

Various efforts are being undertaken to address the severe organ shortage. The utility ratio of the lungs of brain-dead donors in Japan (Fig. 4) is indeed much higher than that reported in the United States. In 2011, the rate of lungs transplanted per deceased donor was 0.39 in the United States [5] and 1.17 in Japan. Despite the aggressive use of marginal lungs by Japanese lung transplant centers, the overall survival of recipients in Japan is generally better than that reported by the International Society for Heart and Lung Transplantation registry (5-year survival, approximately 50 %) [1]. Elaborations to make full use of marginal brain-dead-donor lungs include lobar transplantation after truncation of an unsuitable lobe and the use of ex vivo lung perfusion. Elaborations to achieve living-donor lung transplantation for donor–recipient combinations considered to be unsuitable are also being undertaken. These include native lung-sparing lobar transplantation using donor lungs smaller than ideal lungs [6] and middle-lobe transplantation for small pediatric chests, which was reported by Okayama University in 2013. Revision of the
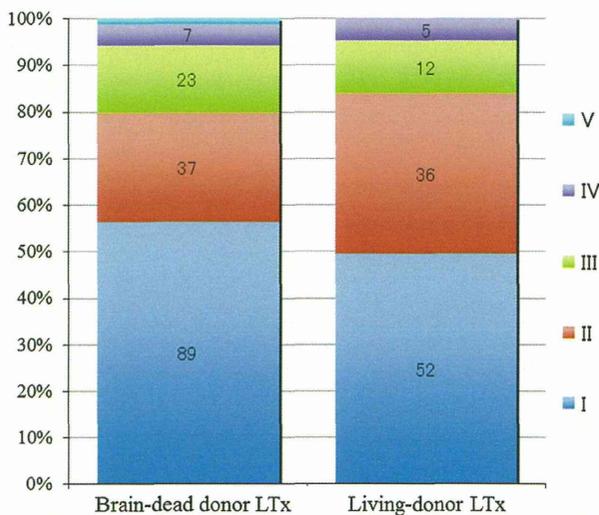

Fig. 8 Hugh–Jones classifications of the lung transplant recipients who survived for >6 months after transplantation. *LTx* lung transplantation

Fig. 9 Daily life status of the lung transplant recipients who survived for >6 months after transplantation. *LTx* lung transplantation
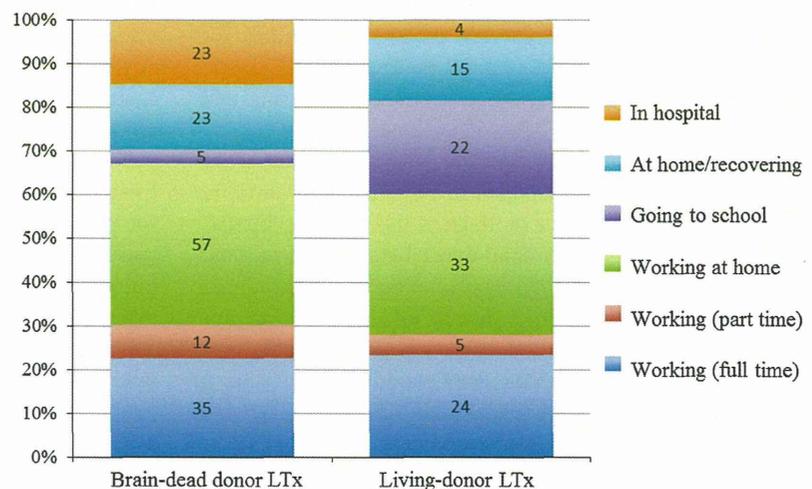
Fig. 10 Causes of death after lung transplantation. *CLAD* chronic lung allograft dysfunction, *PTLD* post-transplant lymphoproliferative disorder
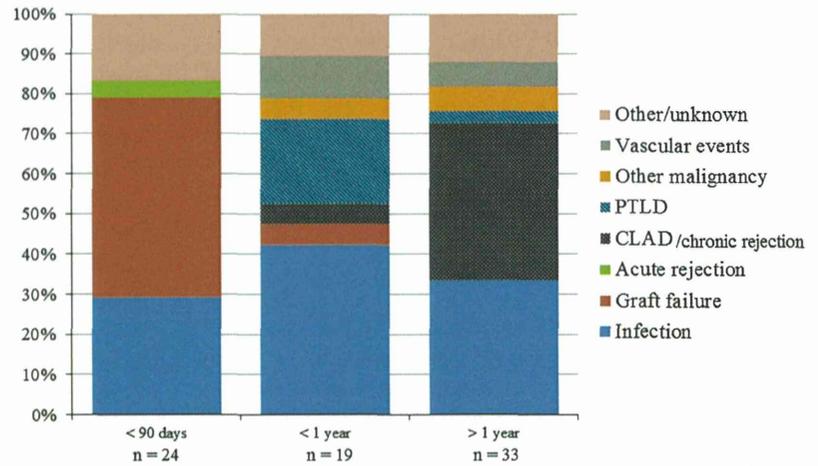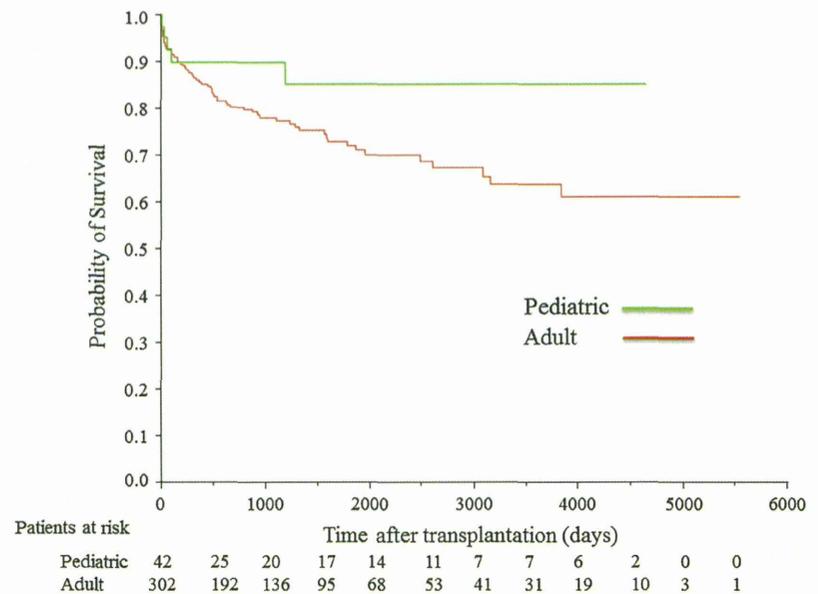

Fig. 11 Survival of pediatric and adult lung transplant recipients

recipient selection criteria for brain-dead-donor lung transplantation may also provide better opportunities for lung transplantation patients on the waiting list with poorer prognoses, such as those with interstitial pneumonia and bronchiectasis.

Notably, the survival difference among different types of lung transplantation in Japan in Fig. 7b might partially reflect severe donor organ shortage in this country. Firstly, among recipients of brain-dead-donor lung transplantation, those who needed bilateral transplantation may be at higher perioperative mortality risks due to infection and/or pulmonary hypertension. For example, a patient with idiopathic interstitial pneumonia who would otherwise be a candidate for single lung transplantation in Japan may need bilateral transplantation for concurrent infection (e.g., *Aspergillus*) and/or secondary pulmonary hypertension,

although the same patient may be a candidate for bilateral transplantation even without such complications in other countries with more abundant donor organs. Secondly, living-donor lung transplantation per se is an option almost unique to Japan due to the severe organ shortage. Because pediatric brain-dead donors are extremely rare in Japan, living-donor lung transplantation is often the only option for pediatric lung transplant candidates. Especially for a small pediatric patient whose chest size cannot accept bilateral adult lobes, the only remaining option is single lobar transplantation, which evidently carries a high risk due to difficult size matching and dependence on the single lobe with limited pulmonary capillary bed. Contralateral native lung may need to be removed to accommodate an over-sized adult lobe into a small chest [7]. This is also a part of aforementioned efforts of Japanese lung transplant

surgeons to save lives of patients with otherwise fatal lung disorders.

Overall, lung transplantation in Japan has gone through important turning points during the last few years. Lung transplant centers in Japan are now required to achieve higher volumes of lung transplantations while continuing efforts to further increase the number of lung transplantations to meet patient demand.

References

1. Stehlik J, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dipchand AI, et al. The Registry of the International Society for Heart and Lung Transplantation: 29th official adult heart transplant report–2012. J Heart Lung Transplant. 2012;31(10):1052–64.

2. 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(10):648–51.

3. Fujimura S, Kondo T. The lung transplantation has come to be done in Japan. Kyobu Geka. 2000;53(12):986–91.

4. Oto T, Okada Y, Bando T, Minami M, Shiraishi T, Nagayasu T, et al. Registry of the Japanese Society of Lung and Heart–Lung Transplantation: the official Japanese lung transplantation report 2012. Gen Thorac Cardiovasc Surg. 2013;61(4):208–11.

5. Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN/SRTR 2011 Annual Data Report. In: Rockville MD, Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation; 2012. p. 149–178.

6. Fujinaga T, Bando T, Nakajima D, Sakamoto J, Chen F, Shoji T, et al. Living-donor lobar lung transplantation with sparing of bilateral native upper lobes: a novel strategy. J Heart Lung Transplant. 2011;30(3):351–3.

7. Date H, Shiraishi T, Sugimoto S, Shoji T, Chen F, Hiratsuka M, et al. Outcome of living-donor lobar lung transplantation using a single donor. J Thorac Cardiovasc Surg. 2012;144(3):710–5.

CASE REPORT

Successful bilateral lung transplantation after 16 h of lung preservation with EP-TU solution: report of a case

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Tetsu Sado · Masafumi Noda · Yasushi Hoshikawa ·
Chiaki Endo · Akira Sakurada · Sumiko Maeda ·
Miki Akiba · Kunihiko Hoshi · Takashi Kondo

Abstract We report a case of bilateral lung transplantation (BLT) after preservation of the donor graft for 16 h 5 min with EP-TU, an extracellular phosphate-buffered lung preservation solution. The recipient was a 26-year-old woman with idiopathic pulmonary arterial hypertension and the graft ischemic time was prolonged significantly because of the time required to induce peripheral veno-arterial extracorporeal membrane oxygenation (V-A ECMO) under local anesthesia, and address the severe intrathoracic and pericardial adhesions from past surgery for partial anomalous pulmonary venous return, with concurrent annular plication of the tricuspid valve. After the operation, ECMO and continuous hemodiafiltration were started preemptively to protect the grafts against excessive edema. Postoperative chest X-ray showed diffuse bilateral infiltrates, which improved within a few days and she was weaned off ECMO on day 9. Successful BLT after a graft ischemic time of over 16 h has rarely been described in clinical lung transplantation.

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Introduction

Lung transplantation has been established as an effective therapeutic strategy for patients with end-stage lung diseases. However, primary graft dysfunction (PGD), primarily caused by ischemia–reperfusion injury of the lung allograft, remains a serious problem, accounting for 26 % of deaths within 30 days of the procedure [1]. Experimental studies have shown that prolonged cold ischemia aggravates lung graft function after reperfusion [2, 3], with lung preservation times of up to 6–8 h generally being accepted as safe by most lung transplant centers. Despite this, allograft ischemic times would be expectedly or unexpectedly prolonged beyond 8 h for recipients with severe pleural, hilar, or pericardial adhesions. We previously reported a positive result of lung preservation after up to 12 h with EP-TU solution, an extracellular phosphate-buffered lung preservation solution [4]. However, ischemic times prolonged for over 12 h have scarcely been reported in clinical lung transplantation. We report a case of successful bilateral lung transplantation (BLT) with an allograft ischemic time of over 16 h with EP-TU lung preservation solution.

Case report

A 22-year-old woman with idiopathic pulmonary arterial hypertension (IPAH) was referred to our hospital for lung transplantation. Partial anomalous pulmonary venous return (PAPVR) had been diagnosed when she was 1 year
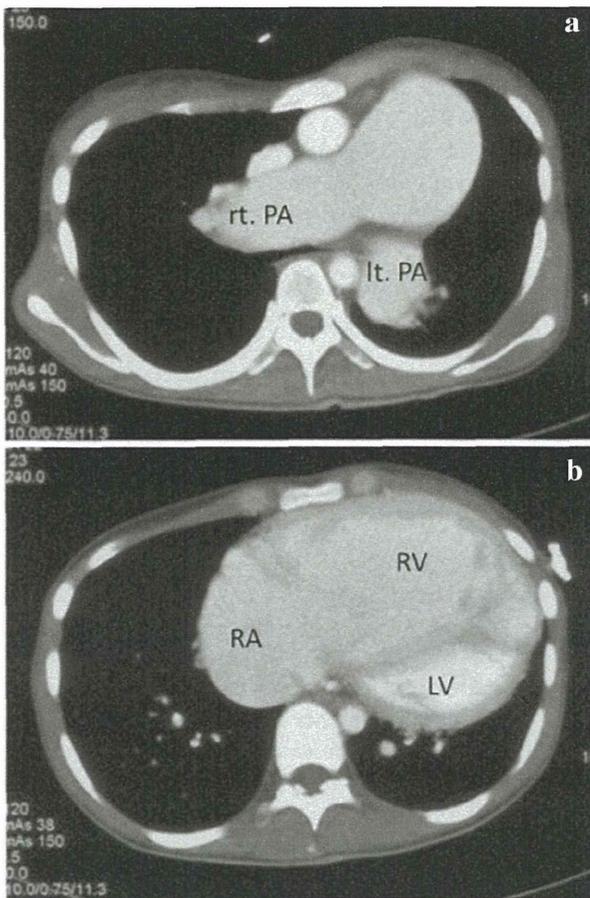
Fig. 1 Chest computed tomography before lung transplantation showed dilatation of the bilateral pulmonary arteries (**a**) and the small left ventricle (**b**) of the recipient. *PA* pulmonary artery, *RA* right atrium, *RV* right ventricle, *LV* left ventricle

old, with the right superior pulmonary vein draining into the superior vena cava (SVC). At 8 years, she underwent intra-atrial route formation from the native SVC orifice to the newly created atrial septal defect to drain the anomalous superior pulmonary vein into the left atrium, using an equine pericardium patch; however, her pulmonary arterial pressure (PAP) continued to increase. When she was 21 years, epoprostenol continuous infusion therapy was started for IPAH, and when she was 23 years, she was put on the wait list for lung transplantation, at which time her functional status was New York Heart Association (NYHA) Class IV. Cardiac catheterization revealed a PAP of 111/60, a right atrial pressure of 20 mmHg, and a cardiac index of 1.48 L/min/m^2. Chest computed tomography scan showed dilatation of the bilateral pulmonary arteries and small left ventricle and left atrium (Fig. 1). Echocardiography revealed severe tricuspid valve regurgitation. We planned to perform BLT with concurrent annular plication of the tricuspid valve and reconstruction of the

recipient PA with a donor aortic homograft [5]. During the waiting time, her abdomen became distended with ascites and she was confined to bed.

At 26 years, she underwent BLT after waiting for a suitable graft for 3 years. The cadaveric donor was a male in his 40s, with an excellent PaO$_2$/FiO$_2$ ratio of over 500 Torr and clear bilateral lung fields on chest X-rays before the organ procurement. The bilateral lung grafts were preserved with EP-TU lung preservation solution [4]. Prior to the induction of general anesthesia in the recipient, peripheral veno-arterial extracorporeal membrane oxygenation (V-A ECMO) was instituted through the right femoral vein and artery using local anesthesia, with some anxiety about collapse of the systemic circulation with mechanical ventilation. General anesthesia was induced and the chest was opened through a bilateral trans-sternal anterior thoracotomy. The right lung was severely adhered to the SVC and pericardium. The heart was also severely adhered to the pericardium and anterior chest wall as a result of the past surgery for PAPVR. Following pericardial dissection, cardiopulmonary bypass (CPB) was initiated. The adhesions between the heart and the anterior chest wall, and then those between the pulmonary veins and the ventricles, were carefully dissected. Exposure of the right superior pulmonary vein was limited by the severe adhesion, so its branches were ligated and transected one by one at the peripheral level. Other structures of the pulmonary hilus were exposed and the bilateral lungs were extracted. The ascending aorta was clamped and cardiac arrest was induced with cold cardioplegia. Annular plication of the tricuspid valve was performed first. At the same time, the lower lobe of the left lung allograft was resected on the back table because of a significant size mismatch between the left pleural cavity and the graft. Transplantation of the left upper lobe and the right lung was then performed. Anastomoses of the pulmonary arteries could be completed in the usual manner following reduction of the pulmonary artery diameters after CPB institution. The inferior pulmonary veins of the recipient were hypoplastic and the donor left atrial cuffs were anastomosed to the recipient superior pulmonary veins. The heart was reperfused upon completion of the BLT. The operating time was 18 h 33 min, the CPB time was 12 h 32 min, the ECMO time prior to CPB institution was 2 h 34 min, and the cardiac arrest time was 3 h 50 min. The ischemic time that the lung graft was subjected to from the cross-clamp of the donor aorta through to reperfusion of the recipient heart was 16 h 5 min. Because of the fear of severe ischemia–reperfusion injury, CPB was switched to V-A ECMO again. The patient's postoperative course was complicated by intra-thoracic bleeding and she underwent re-thoracotomy 12 h after admission to the intensive care unit (ICU). Continuous hemodiafiltration (CHDF) was started immediately
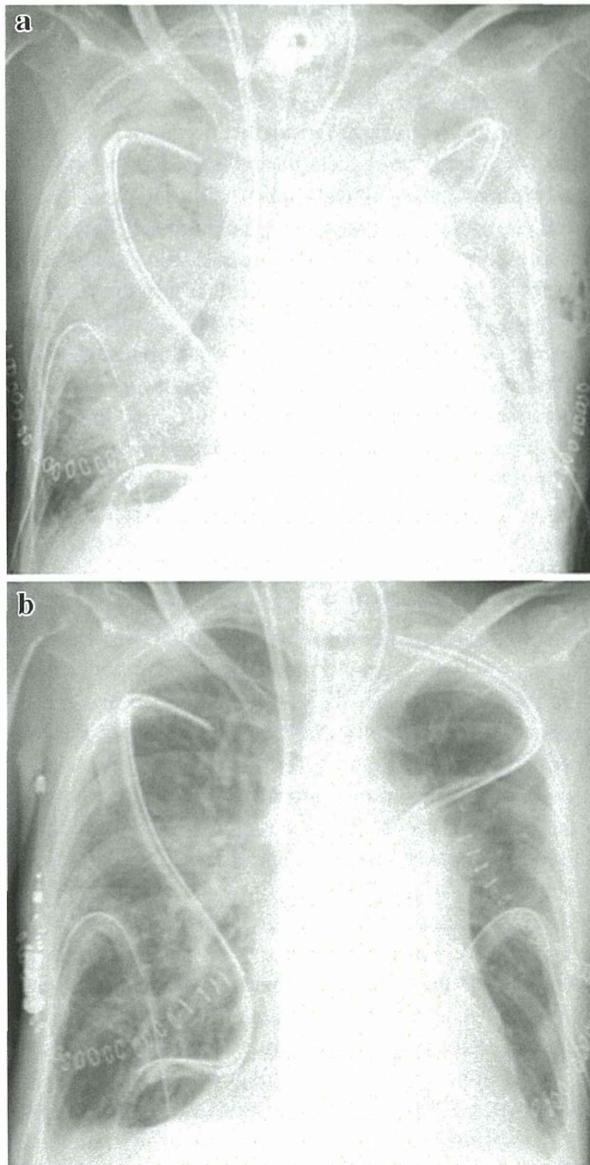
Fig. 2 a Chest X-ray on intensive care unit admission after lung transplantation showed diffuse bilateral infiltrates, indicating severe ischemia–reperfusion injury of the bilateral lung grafts. **b** Chest X-ray on day 3 after lung transplantation showed marked improvement of bilateral infiltrates

after the re-operation. The chest X-ray in the early phase after lung transplantation showed diffuse bilateral infiltrates (Fig. 2a), indicating severe ischemia–reperfusion injury of the bilateral lung grafts; however, this improved within a few days in response to ECMO support (Fig. 2b). After refilling of systemic circulation, aggressive fluid removal by ultrafiltration and frequent postural drainage were started and the lung edema improved further. The patient was weaned off ECMO on day 9 after the operation,

when impaired left ventricular function showed adequate recovery. She was weaned off mechanical ventilation on day 17 and discharged from the ICU on day 30. She is currently well with no activity limitations 3 years after the procedure. She has experienced no episodes of acute rejection and her FEV1.0 is stable at about 2.11 L (73 % of predicted value). She can now walk 543 m in 6 min.

Discussion

The impact of graft ischemic time on early graft function and survival after lung transplant recipients remains controversial. Recent clinical studies on a large cohort of patients have demonstrated close relationships between graft ischemic time and early gas exchange, risk of PGD, and long-term survival after lung transplantation. Thabut and coauthors reported a steep increase in the relative risk of death when the graft ischemic time was longer than 6 h in their analysis of 505 lung transplant patients in the French Lung Transplantation Group [6]. They estimated that the relative risk of death by 90 days postoperatively with a 6-h graft ischemic time vs. a 2-h graft ischemic time was 1.98. Kuntz and coauthors found that the adjusted odds ratio for PGD increases by 1.25 per h of ischemic time when the graft ischemic time is longer than 3 h, in their analysis of 6984 recipients in the database of the United Network for Organ Sharing and International Society for Heart and Lung Transplantation Registry [7]. Given those findings, shorter ischemic times are desirable to minimize the risk of PGD and optimize the chance of survival for lung transplant recipients. In the present case, the graft ischemic times were prolonged significantly because of the time needed for induction of ECMO with local anesthesia, for dealing with severe intrathoracic and pericardial adhesions from the past surgery for PAPVR, and for applying annular plication for severe tricuspid valve regurgitation. The graft ischemic time from cross-clamping of the donor aorta through to reperfusion of the recipient heart was 16 h 5 min, which is by far the longest in our experience and has rarely been reported in clinical lung transplantation anywhere in the world. We have previously used EP-TU lung preservation solution with good early graft function and patient survival obtained after preservation times of up to 12 h [4]. EP-TU solution is an extracellular phosphate-buffered solution with 2 % dextran 40 and 1 % glucose. By using this solution, successful lung preservation for up to 96 h was demonstrated in a canine lung transplant model [8]. Recent clinical studies have also demonstrated the superiority of extracellular fluid type lung preservation solutions over intracellular fluid types [9] and the use of EP-TU solution obviously served as one of the keys to the successful outcome. Other factors that possibly