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ORIGINAL ARTICLE

Clinical application of ET-Kyoto solution for lung transplantation

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Abstract Because of the severe donor shortage in Japan, even after the revision of the Organ Transplant Law in 2010, the frequency of recovery of extended criteria lungs has increased in Japan. We developed a new lung preservation solution, "ET-Kyoto solution," to enhance lung preservation, to minimize primary graft dysfunction (PGD) and to improve the post-transplant outcomes. In this study, we retrospectively analyzed our results of lung transplantation using the ET-Kyoto solution. From 2002 to 2012, 26 patients underwent transplantation of lungs preserved with ET-Kyoto solution from brain-dead donors. We retrospectively reviewed the post-transplant pulmonary function and long-term survival. The graft performance was assessed by the PGD grading system. The mean graft ischemic time was 483.8 ± 19.0 min. The oxygenation capacity after reperfusion and recovery of respiratory function were both acceptable despite the long ischemic time. The survival rate at 5 years after transplantation was 85.1 %. Lungs preserved by ET-Kyoto solution had satisfactory postoperative lung function, despite the long preservation time, with excellent long-term survival. The results were acceptable for the use of grafts with a long ischemic time.

Keywords Deceased donor · ET-Kyoto solution · Japan · Long ischemic time · Lung transplantation · Primary graft dysfunction

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Introduction

Lung transplantation is an accepted therapeutic option for patients with various respiratory diseases at the terminal stage. However, the donor organ shortage continues to be a critical problem worldwide. Particularly in Japan, the problem has been much more serious, as the annual number of deceased donors was only 0.9 per million population in 2010, whereas in most European countries and the USA, the numbers were 10–30 per million, and were five to 10 per million in other Asian countries [1]. To relieve this problem, the Japanese Organ Transplant Law was amended in 2010. After the revision, the number of brain-dead donors dramatically increased, but remained insufficient for the needs of the waiting candidates [2]. Therefore, Japanese lung transplant programs have aggressively accepted extended criteria donor lungs, and the recovery rate from brain-dead donors rose to as high as 63 % [2]. Moreover, lung grafts have been subjected to long ischemic times, with the average being 472 min [3]. In such an unfavorable situation, improvements in lung preservation were crucial to minimize the primary graft dysfunction (PGD) resulting from ischemia–reperfusion injury. We developed an original lung preservation solution, "ET-Kyoto solution", which contains trehalose, that has a protective effect on preserved lungs [4], and have used it for lung preservation in our lung transplant program [5]. In this

study, we retrospectively examined the results of lung transplantation using the ET-Kyoto solution for lung preservation.

Patients and methods

During the first 11 years after the lung transplantation program started in Kyoto University Hospital, from April 2002 to December 2012, 63 patients underwent lung transplantation, and the ET-Kyoto solution was used for preservation of the lungs transplanted into 61 patients. Of the 61 patients, 26 received lung transplantations from brain-dead donors and 35 from living lung donors. Because this study was focused on the preservative effect of ET-Kyoto solution on pulmonary grafts after long ischemia, we excluded living-donor lobar lung transplantation from the analysis because of the short ischemic times, which ranged from 77 to 252 min. We evaluated the post-transplant pulmonary function and long-term survival in the 26 recipients of brain-dead donor lung transplants. We reviewed and collected data from the medical records of the patients retrospectively. All patients had previously provided consent for use of their clinical data for research. This study observed the procedures outlined in the 2000 Declaration of Helsinki and the 2008 Declaration of Istanbul, and was approved by the Institutional Review Board of Kyoto University.

The severity of PGD at 12, 24, 48, and 72 h after transplantation was graded according to the grading system defined by the International Society of Heart and Lung Transplantation [6]. The oxygenation capacity was evaluated by the arterial oxygen tension/inspired oxygen fraction (P/F ratio). We also analyzed the preoperative, surgery-related and postoperative factors. The preoperative factors included the donor and recipient age, indications for transplantation, time on the waiting list prior to the transplant and the donor P/F ratio before the recovery of the donor lung. The surgery-related factors were the procedure types, length of the operation, duration of extracorporeal circulation (ECC), such as cardiopulmonary bypass (CPB) and extracorporeal membrane oxygenation (ECMO), and the graft ischemic time. The postoperative factors included the P/F ratio immediately after reperfusion or after weaning from ECC when used, and the length of stay in the intensive care unit (ICU). All recipients received postoperative immunosuppression with standard triple drug therapy consisting of cyclosporine or tacrolimus, azathioprine or mycophenolate mofetil, and corticosteroids. Acute rejection was treated with a bolus injection of methylprednisolone.

The graft ischemic time and P/F ratio were expressed as the mean ± standard error of the mean (SE). Survival curves were calculated by the Kaplan–Meier method from the day of the operation until death or the day of the most recent follow-up (censored). Fisher's exact test was used for comparisons of categorical variables, and an unpaired two-tailed t test was used for continuous data. The statistical analysis was performed using the StatView 4.5 software program (Abacus Concepts, Berkeley, CA, USA).

Results

The characteristics of the transplant recipients are shown in Table 1. Their mean age was 38.8 years (range 17–56 years), which was younger than that cited in the international registry report [7]. The main indications for deceased donor lung transplantation were emphysema, lymphangioleiomyomatosis, bronchiolitis obliterans, and bronchiectasis. The number of patients with pulmonary fibrosis was small because most of the fibrosis patients had died while on the waiting list. The mean waiting time to the transplant was 852 days (range 295–2574 days). The mean age of the deceased donors ($n = 26$) was 44.5 years (range 21–68 years), and 35 % ($n = 9$) of the deceased donors were older than 50 years. The deceased donors in Japan were older than in other countries [7].

Table 2 shows the perioperative factors. The average operation lasted about 8 h, and half of the recipients required ECC during transplantation, with a mean time of 290 min. Although the mean P/F ratio of the donors was 458.4, 22 out of 25 donors (88 %) were extended criteria donors who did not meet the standard criteria for lung donation. The mean graft ischemic time (38 grafts in 26 patients) was 483.8 ± 19.0 min, and 18 % ($n = 7$) of the grafts were subjected to a long ischemic period of more

Table 1 Characteristics of the lung transplant recipients

Age (years)	38.8 (17–56)		
Sex			
Male	16		
Female	10		
Diagnosis	Single lung ($n = 12$)	Bilateral ($n = 14$)	Total ($n = 26$)
Emphysema	5	1	6
Lymphangioleiomyomatosis	3	2	5
Bronchiolitis obliterans	2	2	4
Bronchiectasis	0	4	4
Pulmonary fibrosis	3	0	3
Pulmonary hypertension	0	2	2
Other	1	1	2
Waiting time to transplant (days)	852 (295–2574)		

Table 2 The perioperative factors

	n	Mean (range)
Length of operation (min)	26	489.9 (283–1116)
ECC time (min)	13	290.3 (113–677)
Graft ischemic time (min)	38[a]	483.8 (294–823)
Donor P/F ratio[b]	25	458.4 (292–603.4)
P/F ratio after reperfusion	24[c]	347.3 (157–525)
ICU stay (days)	24[d]	9.7 (3–23)

ECC extra corporeal circulation

[a] Number of grafts

[b] P/F ratio: arterial oxygen tension/inspired oxygen fraction

[c] Excluding two patients who required ECC support after reperfusion

[d] Excluding two patients who died in the ICU

than 10 h (Fig. 1). Despite the long ischemic period, the mean P/F ratio after reperfusion in the 24 recipients who were weaned from ECC after implantation was 347.3, and 65 % ($n = 17$) of the recipients had a satisfactory oxygenation capacity with a ratio greater than 300 (Fig. 2). In addition, the P/F ratios of six recipients whose graft ischemic time was longer than 10 h were also relatively good, and there were no significant differences in the P/F ratios between recipients with an ischemic time less than 10 h (360.3 ± 24.3, $n = 18$) and those with an ischemic time longer than 10 h (308.0 ± 30.0, $n = 6$; $p = 0.37$).

Two of the 26 patients died in the ICU: one of them died of uncontrollable bleeding on the first postoperative day, and the other died from serious brain damage caused by intraoperative cerebral ischemia on the 217th postoperative day. The average length of ICU stay of the remaining 24 patients was 9.7 days. The PGD grades at twelve, 24, 48 and 72 h after transplantation are shown in Fig. 3. At 12 h after the operation, 65 % ($n = 17$) of the patients had PGD grade 0, while 19 % ($n = 5$) had grade 3. Thereafter, the graft function improved gradually, and PGD grade 0 was

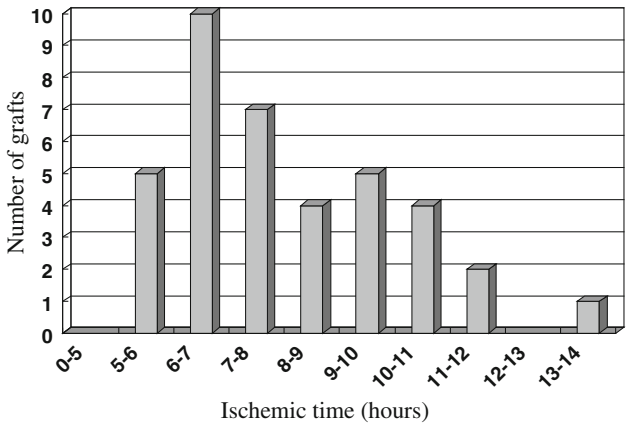

Fig. 1 The number of grafts divided according to the ischemic time

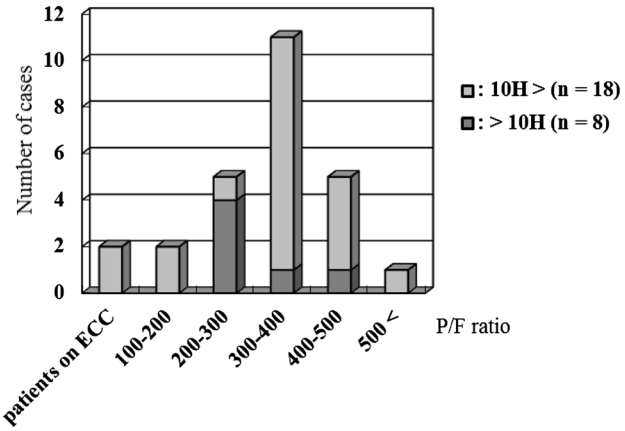

Fig. 2 The number of recipients divided according to the arterial oxygen tension/inspired oxygen fraction (P/F ratio) after reperfusion. Two patients were unable to be weaned from extracorporeal circulation (ECC). The P/F ratios of six recipients who had a graft ischemic time longer than 10 h are shown by *open bars*

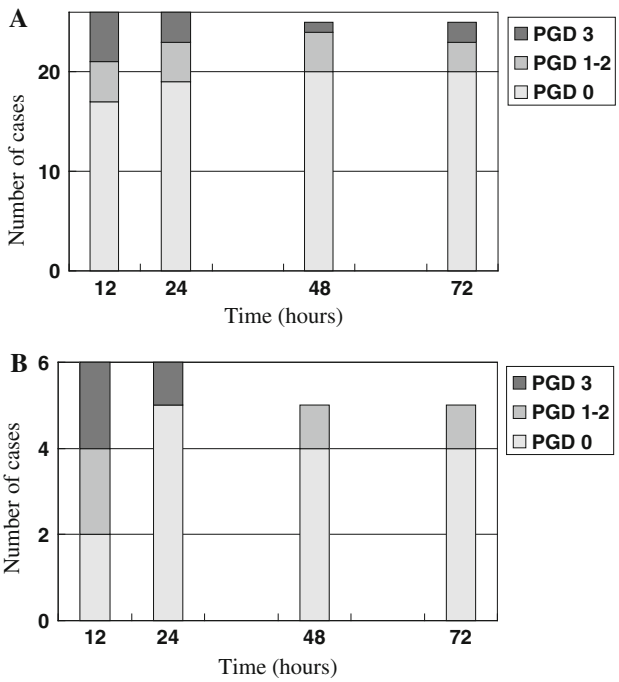

Fig. 3 The primary graft dysfunction (PGD) grade distribution among recipients at specific postoperative time points (**a**). The PGD grade distribution among the six recipients who had a graft ischemic time longer than 10 h (**b**)

seen in 80 % of the patients ($n = 20$) at 48 and 72 h, respectively, after reperfusion. In the six patients who received lungs with an ischemic time longer than 10 h, only two (33 %) of the recipients had PGD grade 0 at 12 h after reperfusion. However, 80 % or more of the patients showed PGD grade 0 after 24 h of reperfusion (Fig. 3b). There were no significant differences in the proportion of patients with grade 3 to patients with grade 0-2 at 12 h after

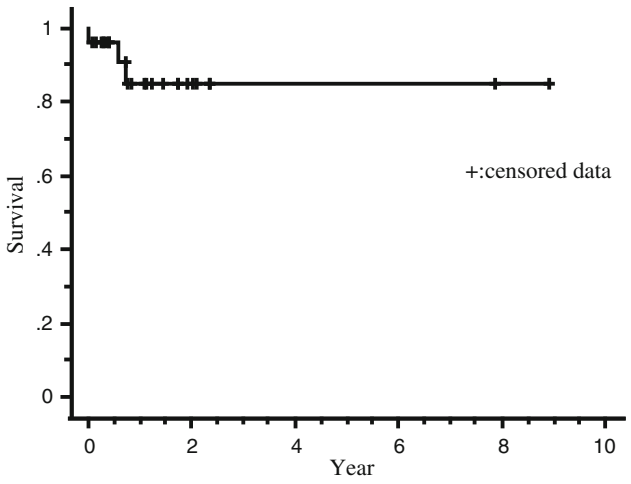

Fig. 4 The Kaplan–Meier survival curve of deceased donor lung transplantation at Kyoto University

reperfusion between the six patients with a long ischemia and the remaining 20 patients ($p = 0.56$). Three of the 26 patients developed chronic lung allograft dysfunction at 5.6, 8.4 and 16.9 months after transplantation, respectively, and were treated by augmentation of the immunosuppression, including bolus injections of methylprednisolone. The overall survival rates for 1, 3 and 5 years after lung transplantation at our institution were all 85.1 % (Fig. 4). These rates were higher than those in the international registry, which were 79, 64 and 53 %, respectively, at 1, 3 and 5 years [7].

Discussion

Although the availability of donor lungs from brain-dead donors increased after the revision of the Japanese Organ Transplant Law in 2010, a donor shortage remains a major limitation of lung transplantation. To extend the donor pool, we developed a new lung preservation solution, ET-Kyoto solution [4], after optimizing the properties of the sugar and the electrolyte contents, as well as providing additives to protect the pulmonary endothelium [8]. In 2009, the ET-Kyoto solution became commercially available (ET-K; Otsuka Pharmaceutical Factory Inc., Naruto, Japan), and has been applied for clinical lung transplantation by other Japanese transplant programs, in addition to that at Kyoto University, with excellent results. Another original lung preservation solution developed at Tohoku University, called the EP-TU solution, also has been widely applied in clinical practice in Japan, and was also reported to be associated with satisfactory post-transplant lung graft function despite a long average graft ischemic time of 483 min [9].

The severe donor shortage drove the Japanese transplant centers to accept extended criteria lungs [2]. In our series, 88 % of donors did not actually meet standard donor criteria. Moreover, the graft ischemic time is longer in Japan than in other countries, partly due to the long transportation time. According to the Transplant Registry Quarterly Data Report of the International Society of Heart and Lung Transplantation [10], the ischemic time in North America was less than 8 h in about 90 % of transplants. The average ischemic time in our series of deceased donor lung transplantation was over 8 h. Additionally, our donors were relatively older than those in North America; 35 % of the donors were over 50 years old in the current study, whereas more than 80 % of donors were reported to be less than 50 years old in North America [10]. Despite the long graft ischemic time, the present retrospective study showed that the ET-Kyoto solution resulted in excellent postoperative graft performance, as indicated by satisfactory oxygenation, PDG grades and long-term survival.

In conclusion, lung transplantation using the ET-Kyoto solution resulted in good postoperative graft function with excellent recipient survival, despite the unfavorable situations presented by the severe donor shortage and the long ischemic time in Japan. Further investigations are needed to evaluate the efficacy of ET-Kyoto solution in clinical practice, because the number of cases in the current study was limited.

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Conflict of interest There is no potential conflict of interest with any companies/organizations whose products or services are discussed in this article.

References

1. Gomez MP, Arredondo E, Paez G, Manyalich M. International registry in organ donation and transplantation 2010. Transplant Proc. 2012;44:1592.
2. Oto T, Okada Y, Bando 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;61:208.
3. Bando T, Date H, Minami M, et al. First registry report: lung transplantation in Japan. Gen Thorac Cardiovasc Surg. 2008;56:17.
4. Bando T, Kosaka S, Liu CJ, et al. Effects of newly developed solutions containing trehalose on 20-hour canine lung preservation. J Thorac Cardiovasc Surg. 1994;108:92.
5. Omasa M, Hasegawa S, Bando T, et al. Application of ET-Kyoto solution in clinical lung transplantation. Ann Thorac Surg. 2004;77:338.
6. Christie JD, Carby M, Bag R, Corris P, Hertz M, Weill D. Report of the ISHLT working group on primary lung graft dysfunction part II: definition. A consensus statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2005;24:1454.

7. Christie JD, Edwards ML, Kucherysvaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report—2012. J Heart Lung Transplant. 2012;31:1073.
8. Wada H, Liu CJ, Hirata T, Bando T, Kosaka S. Effective 30-hour preservation of canine lungs with modified ET-Kyoto solution. Ann Thorac Surg. 1996;61:1099.
9. Okada Y, Matsumura Y, Date H, et al. Clinical application of an extracellular phosphate-buffered solution (EP-TU) for lung preservation: preliminary results of a Japanese series. Surg Today. 2012;42:152.
10. ISHLT Transplant Registry Quarterly Reports for Lung in North America, in ISHLT. http://www.ishlt.org/registries/quarterlyDataReportResults.asp?organ=LU&rptType=tx_char&continent=4. Accessed 7 Oct 2013.