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ORIGINAL ARTICLE

Lung transplantation via cardiopulmonary bypass: excellent survival outcomes from extended criteria donors

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Abstract

Objectives The role of intraoperative cardiopulmonary bypass (CPB) in lung transplant (LTx) surgery is controversial. CPB enables slow pulmonary reperfusion and initial ventilation with low oxygen concentrations, both theoretically protective of transplanted lungs. In this study, we explored clinical outcomes following extended criteria donor LTx surgery implementing a thoroughly protective allograft reperfusion strategy using CPB.

Methods Thirty-nine consecutive adult patients who underwent bilateral LTx with elective CPB and protective allograft reperfusion were reviewed. Bilaterally implanted lungs were reperfused simultaneously, via slow CPB flow reduction and initial ventilation with 21% oxygen and nitric oxide, followed by a brief modified ultrafiltration. During weaning from CPB, mean pulmonary arterial pressure was strictly maintained at 10–15 mmHg by controlling CPB and pulmonary flow. The clinical outcomes in 23 patients who received lungs from extended criteria donors (ECD group) were elucidated and compared to 16 patients undergoing LTx from standard criteria donors (SCD group).

Results No life-threatening deterioration was observed to graft functionality during the first 72 h after LTx in the ECD group; however, only one patient required post-transplant extracorporeal membrane oxygenation. In three of 23 ECD LTx patients (12%), surgical revision for bleeding was required. Survival outcomes for the ECD group were favorable, with 100% survival at 6-months, 87.0% at 1-year, and 80.7% at 5-years. Outcomes in the ECD group were comparable to those in the SCD group.

Conclusions Despite a certain extent of risk associated with full-dose heparinization, use of CPB does not undermine survival outcomes after ECD LTx surgery if protective allograft reperfusion is securely performed.

Keywords Lung transplantation · Cardiopulmonary bypass · Protective allograft reperfusion · Extended criteria donor

Introduction

Lung transplantation (LTx) is regarded as an effective treatment for end-stage lung disease. However, LTx is limited by a persistent shortage of donor organs. In Japan, approximately 300 candidates are continuously listed, yet less than 50 patients receive brain dead donor lungs annually. Consequently, the average waiting time is more than 800 days, resulting in a waiting-list-mortality-rate of approximately 50% [1, 2]. Therefore, living-related LTx is still necessary to save critically ill transplant candidates [1, 2]. The current situation also compels transplant centers in Japan to utilize more than 70% of the offered lungs, in which 90% of the cases were from extended criteria donors [3]. Extending the donor lung criteria may increase LTx, and even small-volume centers are demanded to utilize extended criteria donor (ECD) lungs. However, as there is no universal consensus on the definition and clinical safety

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of LTx from ECDs [4–7], maximal effort is needed to maintain outcomes after ECD-LTx, to ensure that patients benefit from the active use of ECD lungs.

Historically, cardiopulmonary bypass (CPB) has been used in LTx surgery in which the patient is not expected to tolerate single lung ventilation during transplantation. CPB use is inevitable in some transplant cases, whilst there are concerns for adverse effects related to blood cell destruction, excessive consumption of coagulation factor, subsequent systemic inflammation, and coagulopathy following CPB in LTx surgery. Indeed, several studies indicated that CPB use was associated with a significantly higher incidence of primary graft dysfunction (PGD) [8–11]. However, there are other research studies that indicate no disadvantage to CPB in LTx [12–16]. Different centers have different CPB protocols, in terms of the type of pump and management strategies such as reperfusion procedures, complicating interpretation of the actual impact of CPB use in LTx. Several reports from high-volume LTx centers recently indicated an advantage of extracorporeal membrane oxygenation (ECMO) as an alternative cardiopulmonary support method. However, CPB generally provides safer, easier and more versatile surgical fields than ECMO, which still justifies surgeons' choice and preference for CPB in some circumstances.

It is widely believed that high-flow graft reperfusion and initial ventilation with high oxygen concentrations and pressure are detrimental to early allograft function after LTx. This clinical perception has been verified in well-designed studies in animals [17, 18]. In addition, compared to quality lungs, ECD lungs tend to be more fragile in terms of vascular permeability, and susceptible to reperfusion injury caused by uncontrolled reperfusion. CPB allows us to meticulously manage graft reperfusion flow and low oxygen concentration (room air) ventilation. Therefore, CPB management policy must be one of the key factors determining early graft outcomes in ECD-LTx. Although the potentially beneficial effects of protective reperfusion and ventilation via CPB are recognized, the actual clinical outcome of CPB protocol prioritizing reperfusion strategy has not been well examined. We adopted a policy of the routine use of CPB and thorough protective allograft reperfusion strategy for bilateral LTx surgery over a certain period of time. In this study, we explored the feasibility of CPB use in ECD LTx where the protective slow-reperfusion strategy was systematically applied.

Patients and methods

Patients and study design

From January 2010 to December 2016, 91 LTx surgeries were performed in Okayama University Hospital. Of these, 45 patients received bilateral LTx from deceased donors. We excluded 6 pediatric cases; the remaining 39 consecutive adult cases (age > 18) were retrospectively analyzed by reviewing their medical records. The study cohort was further classified into two groups: the standard criteria donor (SCD) group and the extended criteria donor (ECD) group. ECD group was defined as donors that had two or more number of the following conditions: (1) age > 55; (2) smoking history > 20 pack-years; (3) final *P*/*F* ratio < 300 mmHg; (4) infiltration on the last chest X-ray; (5) abnormal secretions at bronchoscopy during evaluation. Those not regarded as ECD were categorized as SCD. Sixteen recipients received lungs from an SCD and 23 from an ECD. All transplants were performed under elective cardiopulmonary bypass. To demonstrate the outcomes of protective CPB strategy on post-transplant outcomes by transplanted donor lung quality, we examined early graft performance and survival outcomes in each group. The institutional review board of Okayama University approved the study (Approval#: 1808-014).

Donor selection and procurement procedure

Available cadaveric lungs were allocated to recipients by the Japan Organ Transplant Network according to waitlist order, ABO compatibility, and predicted pulmonary function value matching. Detailed donor data, including past medical history and examination results, were obtained by authorized donor coordinators. An experienced transplant physician, delegated by the transplant network as a consultant for donor management, was involved from the early stages of the allocation process; the physician collected updated donor information about physical, radiological, and bronchoscopic findings, and helped the local donor hospital staff optimize donor condition as much as possible. The final decision on donor selection was made by our experienced transplant physicians. Lung procurement was standardized. The lungs were removed en bloc after antegrade perfusion (60 ml/kg; 4 °C, 30 cmH_2O). Donor lungs were routinely flushed with extracellular phosphate-buffered lung preservation (EP-TU) solution ® (Cell Science & Technology Institute, Sendai Japan) with added prostaglandin. After returning the lungs to the recipients' hospitals, additional retrograde perfusion was performed through the pulmonary veins to optimize lung graft preservation.

Lung transplantation procedure

Procedure indication was determined for each candidate according to their primary disease, urgency, and organ availability. Bilateral LTx was limited to cases in which recipients could not accept single LTx due to medical problems, such as airway infection or comorbid pulmonary hypertension. After hilar preparation was completed, cardiopulmonary

support was routinely established. Following bilateral pneumonectomy, donor lungs were implanted in order of the difficulty of anastomoses, with the hardest (commonly left side) first. The heart is kept beating throughout the implantation procedure. During implantation of the second lung, the first lung was not reperfused (the hilum remained clamped), and crushed ice was placed in the chest cavity to topically cool the first lung. After bilateral lung-implantation was complete, both lungs were reperfused simultaneously, following methylpredonisolone administration, and the patient was weaned from CPB. Regarding the surgical techniques for implantation, an end-to-end anastomosis with a single running suture was performed in the following order: bronchus, pulmonary vein, and pulmonary artery. Recipients received a triple-drug maintenance immunosuppressive regimen consisting of a calcineurin inhibitor (cyclosporine or tacrolimus), mycophenolate mofetil, and steroids.

Cardiopulmonary bypass

CPB was established by ascending aortic and right atrial cannulation. The pulmonary artery was vented if right ventricle and pulmonary arteries distended (commonly in patients with pulmonary arterial hypertension). We used a hollow-fiber membrane oxygenator (RX-25; Terumo, Tokyo), open hard-shell reservoir (Capiox-RX; Terumo, Tokyo), arterial filter (CX-AF125; Terumo, Tokyo), and roller pump perfusion (S-5; LivaNova, Munich, Germany). The CPB circuits were primed with Ringer's acetate solution, albumin, and mannitol. Anticoagulation via intravenous heparin was used to maintain an activated clotting time of over 400 s during CPB. The initial CPB flow rate was 2.4 L/min/m^2. Perfusion pressures were maintained at 60–80 mmHg, systemic temperatures at 34 °C, and hematocrits at more than 25% by adding packed red blood cells. Pump suckers were turned off when the bronchus was opened. Cell Saver was not used at all.

Protective allograft reperfusion strategy

Systemic rewarming was initiated and 20 mg/kg of methylprednisolone was administered at the end of the anastomosing procedure for the second lung. After completion of bilateral implantation, we reperfused the bilateral lungs simultaneously. Mean pulmonary artery pressure (PAP) was strictly maintained at 10–15 mmHg by thoroughly controlling the CPB and pulmonary flow. Mechanical ventilation was initiated with the pressure control mode setting, an inspired oxygen fraction (FiO_2) of 21%, peak inspiratory pressure of 20–25 cmH_2O, end expiratory pressure of 5–10 cmH_2O, respiratory rate of 12 breaths/minute, and tidal volume of 6–8 ml/kg of ideal body weight. Nitric oxide (20 ppm) was also administered intratracheally. After 10–15 min of reperfusion, we slowly weaned the patient from CPB. The CPB flow was reduced in a stepwise fashion over > 30 min. Following weaning from CPB, we performed 10 min of modified ultrafiltration (MUF) to remove the initial cytokines and any excess fluid emitted from the reperfused lung allografts and the heart [19]. After completing MUF, the arterial and venous cannulae were removed. The FiO_2 ventilator setting was adjusted to maintain an arterial blood gas saturation of > 90%. Maximal effort to avoid using extracorporeal support after reperfusion was made in all cases. We only introduced extracorporeal membrane oxygenation (ECMO) when the artery blood gas saturation remained < 90% (FiO_2 100%, PIP > 30 cmH_2O) for > 30 min after the start of weaning off CPB.

Statistical analysis

All data are presented as medians and ranges. Categorical data are presented as frequencies (percentages). Chi square (χ^2) tests or Mann–Whitney U tests were used to evaluate the differences in continuous variables between the groups. Kaplan–Meier statistics with log-rank testing were used for survival analyses. Probability (p) values of < 0.05 were considered statistically significant. PGD grade was defined in accordance with the International Society for Heart and Lung Transplantation working group statement [25]. To determine the pre-transplant severity of each patient, their US lung allocation score (LAS) was retrospectively calculated (in November 2016) using the LAS calculator available on the OPTN website (https://optn.transplant.hrsa.gov/resources/allocation-calculators/las-calculator/). The donor score was defined according to the previous study by Oto et al. [21]. In brief, the scoring system includes five domains representing known important donor criteria, i.e., age, smoking history, chest radiography, secretions, and the ratio of arterial oxygen tension to inspired oxygen fraction (P/F). Each variable is graded between 0 and 3, with the exception of the P/F factor, which is given a double-weighting (graded 0–6) because of its perceived clinical significance. The score was applied to grade each donor lung quality objectively. All data were analyzed using SPSS software for windows version 22 (SPSS Inc, Chicago, IL).

Results

Donor and recipient characteristics

The donors' characteristics are given in Table 1; ECD accounted for 59.0%. Median age was significantly higher in the ECD than SCD group. Lung oxygenation of the ECD at different time points was significantly worse than the SCD group. Radiological/bronchoscopic findings indicating

pulmonary edema or infection of the donors were also frequently observed in the ECD group. Donor lungs in the ECD group marked statistically higher donor score than SCD indicating objectively-rated poor quality. There were no significant differences between the ECD and SCD groups in terms of donor gender, body mass index, smoking history and duration of mechanical ventilation. The recipients' characteristics are given in Table 2. The ECD group had 16 recipients (69.6%) with pre-transplant pulmonary hypertension (mean PAP > 25 mmHg), which was similar proportion to the SCD group with 13 (81.3%). The ECD group included 6 recipients (26%) with idiopathic pulmonary arterial hypertension as an indication for transplant. There were no significant between-group differences in terms of recipient age, waiting list time, or LAS.

Intraoperative parameters

There were no cases in which *ex vivo* lung perfusion (EVLP) was applied to the offered lungs. The intraoperative data from the ECD and SCD groups are described in Table 3. Mean PAP after reperfusion was successfully controlled at the targeted level in both groups. Equivalent total CPB times and FiO_2 levels after CPB removal were required. A mean of 55 and 48 min were spent weaning from CPB after allograft reperfusion in the ECD and SCD groups, respectively. The graft ischemic time extended beyond 9 h, and a certain amount of blood product transfusion was required both in the ECD and SCD group: 16/14 units of red blood cell concentrate ; 10/6 units of fresh frozen plasma, respectively. Mean amount of intraoperative bleeding was 3450 (1200–10,410) mL in the ECD and 2340 (970-12060)mL in the SCD group. In all of the > 3000 mL cases, broad pleural adhesion was found. No statistical differences were observed in all of those factors between the groups.

Early graft outcomes

The early performance of grafts is given in Fig. 1. The PaO_2/FiO_2 ratio in the ECD group showed no significant changes during the first 72 h after LTx (fluctuating around 300); there were also no significant between-group differences. Other indicators of early post-transplant outcomes are given in Table 4. Grade 3 PGD developed in 17% of patients in the ECD group. Three ECD recipients underwent single surgical revision for postoperative bleeding and recovered thereafter. There was only one patient in the SCD group who required ECMO after LTx, but this patient successfully recovered within a short time period. No recipients required postoperative hemodialysis or hemofiltration to resolve a systemic condition associated with primary graft dysfunction. The early outcomes after LTx in the ECD were comparable to the SCD group in PGD grades, postoperative ventilator support times, necessity for extracorporeal membrane oxygenation support, or intensive care unit or hospital stays. The length of hospital

Table 1 Donor characteristics

	ECD ($n=23$)	SCD ($n=16$)	p value
Age (years)	49 (20–69)	43 (27–71)	0.489
Age > 55	9 (39%)	4 (40%)	0.357
Female gender	10 (43%)	7 (44%)	0.987
BMI (kg/m^2)	23.5 (17.5–39.5)	22.4 (16.9–39.8)	0.944
Smoking history	12 (52%)	10 (63%)	0.522
Smoking > 20 pack-years	7 (30%)	2 (13%)	0.191
Ventilation duration (day)	6 (1–20)	5 (3–13)	0.601
P/F ratio at final evaluation	388 (111–548)	479 (307–566)	0.028
P/F ratio at final evaluation < 300	6 (26%)	0	0.026
Best *P/F* ratio	424 (118–602)	512 (391–591)	0.040
Best *P/F* ratio < 300	5 (22%)	0 (0%)	0.045
Worst *P/F* ratio	340 (111–470)	357 (245–540)	0.095
Worst *P/F* ratio < 300	10 (43%)	4 (25%)	0.237
Abnormal chest X-ray	20 (87%)	2 (13%)	< 0.001
Massive secretions on bronchoscopy	14 (61%)	1 (7%)	< 0.001
Evidence of non-resident bacteria in sputum culture	8 (34.8%)	1 (6.3%)	0.038
Donor score	8 (4–12)	3 (1–8)	< 0.001

Categorical data are presented as number (%) and continuous data as median (range)

BMI body mass index, *ECD* extended criteria donor, *P/F* partial pressure of arterial oxygen to fraction of inspired oxygen, *SCD* standard criteria donor

Table 2 Recipient characteristics

	ECD ($n=23$)	SCD ($n=16$)	p value
Age (years)	38 (21–61)	51 (23–57)	0.061
Female gender	14 (61%)	7 (44%)	0.291
BMI (kg/m^2)	17.7 (11.9–23.9)	21.1 (13.6–29.6)	0.011
Re transplantation	2 (8%)	0 (0%)	0.228
Time on waiting list (days)	538 (45-3331)	419 (40-2167)	0.746
LAS	38.2 (30.2–69.2)	41.3 (33.5–55.5)	0.621
Comorbid pulmonary hypertension			
Mean PAP 25–35 mmhg	11 (48%)	8 (50%)	0.894
Mean PAP > 35 mmhg	5 (22%)	5 (31%)	0.503
Diagnosis			
Idiopathic interstitial pneumonia	2 (9%)	7 (44%)	0.011
Idiopathic pulmonary arterial hypertension	6 (26%)	1 (6%)	0.112
Bronchiolitis obliterans	6 (26%)	1 (6%)	0.112
Bronchiectasis	3 (13%)	3 (19%)	0.339
Lymphangioleiomyomatosis	2 (9%)	2 (13%)	0.700
Diffuse panbronchiolitis	3 (13%)	1 (6%)	0.492
Pulmonary emphysema	1 (4%)	0 (0%)	0.398

Categorical data are presented as number (%) and continuous data as median (range)

BMI body mass index, *ECD* extended criteria donor, *LAS* lung allocation score, *PAP* pulmonary artery pressure, *SCD* standard criteria donor

Table 3 Intraoperative data

	ECD ($n=23$)	SCD ($n=16$)	p value
Number of pre-transplant EVLP use	0	0	NA
Mean PAP (mmHg)			
Pre-CPB	28 (18–60)	31 (23–51)	0.128
Re-perfusion	11 (8–17)	13 (10–16)	0.738
Post-CPB	21 (13–30)	21(16–27)	0.641
FiO_2 (%)			
Re-perfusion	21	21	NA
Post-CPB	55 (40–100)	45 (40–100)	0.143
CPB time (min)	258 (195–409)	264 (217–364)	0.388
Time from reperfusion to CPB off (min)	54 (27–90)	50 (30–82)	0.621
Ischemic time left lung (min)	553 (267–747)	569 (353–787)	0.582
Ischemic time right lung (min)	557 (277–747)	563 (353–787)	0.563
Bleeding (mL)	3450 (1200–10,410)	2340 (970-12060)	0.159
RBC (unit)	16 (6–44)	14 (6–50)	0.128
FFP (unit)	10 (6–16)	6 (4–18)	0.010
PC (unit)	30 (6–40)	20 (0–35)	0.008

Categorical data are presented as number (%) and continuous data as median (range)

CPB cardiopulmonary bypass, *ECD* extended criteria donor, *EVLP* ex vivo lung perfusion, *FFP* fresh frozen plasma, *FiO_2* fraction of inspired oxygen, *PAP* pulmonary artery pressure, *PC* platelet concentrates, *RBC* red blood cells, *SCD* standard criteria donor

stay in the SCD group was paradoxically longer than in the ECD group because of four patients with extremely prolonged hospitalization. Of them, three patients developed impaired airway or skin healing that required repeated medical or surgical interventions. The remaining one

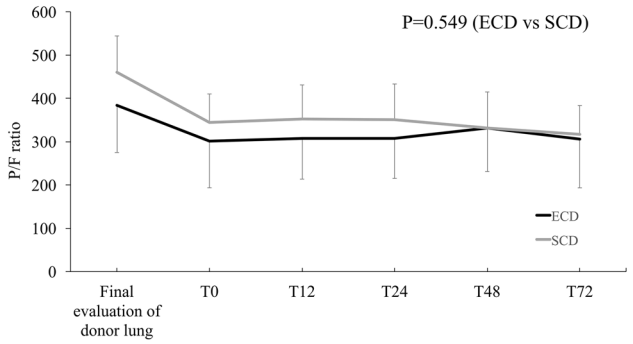

Fig. 1 Graft function early after LTx surgery in the extended and standard criteria donor groups. *P/F* partial arterial oxygen pressure/fraction of inspired oxygen, *ECD* extended criteria donor, *SCD* standard criteria donor, *T0* at intensive care unit arrival, *T12-T72* 12–72 h after intensive care unit admission.

Table 4 Postoperative data

	ECD ($n=23$)	SCD ($n=16$)	p value
PGD			
0–2	19 (83%)	14 (88%)	0.120
3	4 (17%)	2 (13%)	0.120
Surgical revision for bleeding	3 (13%)	2 (13%)	0.960
Posttransplant ECMO use	0	1 (6%)	0.225
Hemodialysis	0	0	NA
Ventilation time (h)	154 (43–827)	76 (21-1704)	0.053
ICU stay (day)	20 (7–71)	22 (5-106)	0.877
Hospital stay (day)	86 (49–366)	112 (53–788)	0.128
Survival (%)			
6 months	100	100	NA
12 months	100	87.5	0.090
24 months	87.0	81.3	0.617
36 months	87.0	81.3	0.617
48 months	87.0	81.3	0.617
60 months	80.7	78.5	0.871

Categorical data are presented as number (%) and continuous data as median (range)

ECD extended criteria donor, *ECMO* extracorporeal membrane oxygenation, *ICU* intensive care unit, *PGD* primary graft dysfunction, *SCD* standard criteria donor

patient developed refractory antibody mediated rejection posttransplant.

Survival outcomes

The survival data are given in Table 4 and Fig. 2. No early mortality occurred. Survival probability was favorable, even in the ECD group, with 100% at 6 months, 100% at 1 year, 87.0% at 2 years, 87.0% at 3 years, and 80.7% at 5 years. Very similar survival outcomes were achieved in the ECD and SCD groups. Six of the 39 recipients died during the observation period; causes of death included malignancy ($n=3$), infection ($n=2$), and chronic lung allograft dysfunction ($n=1$). There were no critical events relevant to CPB.

Discussion

In this feasibility study regarding the specific CPB strategy for LTx surgery, ECD lungs provided a feasible short-term outcome and an excellent long-term outcome after LTx using CPB. The survival probability of the ECD-LTx population was favorable with 100% at 6-months and 87% at 3-years. We had a consistent recipient/donor selection policy, uniform post-transplant management protocol, and single surgical team throughout the study period. In addition, the study cohort comprised 39 adult bilateral cadaveric LTxs that accounted for 30% of bilateral cadaveric LTx cases performed over the same period in Japan ($n=134$). There were no differences to the SCD group in terms of graft ischemic times, primary diagnoses or severity of recipients' pre-transplant physical conditions. Despite the fact that a certain amount of blood product transfusion was required due to full heparinization, there was no serious morbidity and mortality related to CPB use in the short or long term. Overall, elective intraoperative CPB continuously has a great potential to play a role in ECD-LTx if a protective allograft reperfusion strategy was carefully performed.

Off-pump sequential LTx is one of the most common procedures for LTx surgery. However, this technique poses some inevitable risks in terms of graft protection. The first implanted lung receives considerable pulmonary artery pressure; as a result, acute right-sided heart failure and hemodynamic collapse can develop during clamping of the pulmonary artery. Increased hydrostatic pressure usually causes severe interstitial and alveolar edema, leading to allograft dysfunction and impaired gas exchange [22]. Rosé et al. [23] suggested that CPB starting after the first graft implantation

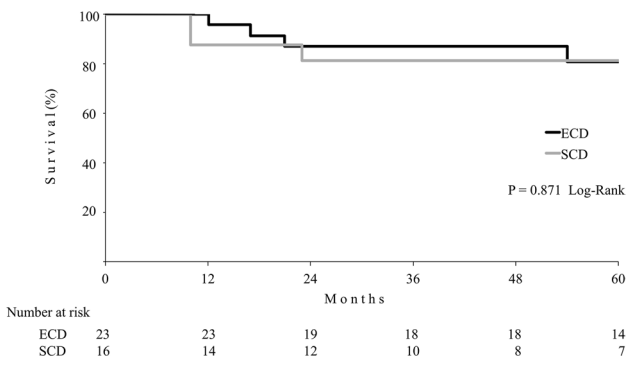

Fig. 2 Survival probability for the 60 months after LTx surgery in the extended and standard criteria donor groups. *ECD* extended criteria donor, *SCD* standard criteria donor

and before the second recipient lung removal appeared to benefit oxygenation and prevent the occurrence of severe pulmonary edema in the first transplanted lung. Furthermore, lung ventilation with highly concentrated oxygen is generally required after reperfusion in off-pump surgery to maintain systemic oxygenation. However, increased FiO_2 in the early phase of reperfusion is also recognized as a strong risk factor for the development of high grade PGD [9]. These adverse effects can occur more frequently in ECD lungs that are increasingly in demand. According to previous research, the use of ECD lungs could affect short-term graft performance despite providing favorable long-term outcomes identical to SCD-LTx [4–7]. Clearly, stabilizing lung graft function as early as possible after LTx is key to successful survival outcomes in ECD-LTx. When prioritizing a perfect control of the initial flow and FiO_2 on transplanted lungs, the sequential transplant technique is not an ideal surgical option.

In the protocol presented here, the first lung was not perfused during the second lung implantation, but rather both sides of the grafts were perfused simultaneously thereafter. When conducting sequential lung reperfusion, it is complicated to manage initial flow or pressure for each implanted lung. The simultaneous reperfusion to bilateral lungs is a simple and optimal manner for perfectly controlled reperfusion despite the need for a tiny prolongation of ischemic time for the first lung. Importantly, the initial pulmonary artery flow was strictly controlled by meticulous CPB flow reduction to maintain an early pulmonary artery pressure of 10–15 mmHg. In addition, CPB support allowed to manage ventilation at a lower FiO_2 level (room air) with nitric oxide inhalation soon after the start of reperfusion, even when early graft function remained unstable. MUF contributed to the minimization of negative influence of CPB use on early systemic and graft conditions. Our protective allograft reperfusion protocol includes multidisciplinary approach comprised all of slow, low-pressurized reperfusion procedure using CPB, nitric oxide inhalation and MUF. Avoiding pressure and oxygen injury in the early phase of reperfusion under controlling adverse effects of CPB may facilitate quick and secure lung graft reconditioning after LTx. Recent EVLP technology provides justification to this; the EVLP protocol, established by a pioneering center, aims to recondition disqualified lung grafts on an *ex vivo* rig, employing careful initial perfusion and ventilation procedures [24] similar in concept to the protective graft reperfusion strategy we performed in vivo after implantation. The management of protective graft reperfusion with CPB may provide a partial alternative to the role of EVLP; of note, in our study, only one patient in the SCD group required post-transplant ECMO, despite the active use of disqualified lungs, and the patients in the cohort experienced neither in-hospital death nor early mortality (< 6 months post-LTx). By following the described protocol, we have rarely encountered critical PGD, even after ECD-LTx.

Nevertheless, there are definite adverse effects associated with the use of CPB, which can contribute toward higher PGD grades after LTx [8–11]. As is often alleged, direct contact between patient blood and foreign substances can cause subsequent systemic inflammatory responses, and anticoagulation during CPB can exacerbate unstable hemostasis in the perioperative period, often demanding a certain amount of blood transfusion or rethoracotomy. As an alternative device for intraoperative cardiopulmonary support in LTx surgery, veno-arterial ECMO has been increasingly utilized with benefits for post-transplant outcomes. Global high-volume centers such as Vienna, Columbia in New York, Pittsburgh, Toronto, Munich and Hannover has recently introduced ECMO as the first-line cardiopulmonary support device in LTx surgery on the basis of their clinical experience with favorable outcomes [25–30]. Arguably, the closed circuit and centrifugal pump, equipped with a well-developed membrane oxygenator (in the recent ECMO system), is theoretically less invasive and reduces inflammatory responses as well as the necessity for full heparinization. However, there is no randomized study designed as ECMO versus conventional CPB to examine a survival benefit from ECMO use. Looking at the past literatures suggesting advantages of ECMO mentioned above, survival rate after LTx with intraoperative ECMO was 96–99% at 1 month, 91–94% at 3 months, and 83–86% at 1 year. When focusing on survival data, comparable or even better outcomes were achieved from our study cohort using CPB.

We would recognize the benefit of ECMO but caution against excessively positive perceptions toward ECMO, regarding it as a universally ideal option. The reason extends beyond a fear of possible air embolisms when dissecting hilum under ECMO circuit. Firstly, flexibility for surgical strategy and optimal visibility of surgical fields are usually limited. ECMO restricts cardiac drainage and manipulation of the heart, resulting in poorer visibility than CPB surgery. Also there is no room for choice of open pulmonary artery or atrial procedure even when the necessity happens. Secondly, the flow generated by the centrifugal pump in ECMO is considerably affected by variability in the patient's circulatory volume. Therefore, ECMO is sometimes unable to control the amount of venous drainage and lung perfusion as intended. By contrast, CPB enables timely volume control with a venous reservoir and strict flow control via a roller pump. These features of CPB allow full drainage of the heart, offering safe, easy and versatile surgical fields as well as meticulous management of pulmonary flow, key to the successful protective allograft reperfusion reviving ECD lungs. A LTx surgery with ECMO is theoretically less invasive but less versatile than with CPB. It necessitates a well-experienced surgeon and stable patients circulatory

conditions. But both are not always available and unpredictable events sometimes happen. Thus universal acceptance of ECMO in LTx surgery should be cautiously gained. The advantage of CPB outweighs the disadvantage in LTx surgery if it is used in the optimal manner. We believe use of elective CPB remains justified if the benefit is maximized by obtaining the most workable surgical situation and carrying out the thorough protective reperfusion strategy.

There are several limitations to our study design. This was a relatively small-scale retrospective research study observing a simple cohort at a single center. The data with a variety of confounding factors such as length of hospital stay and long-term survival rate should be carefully interpreted. We did not directly compare patients with and without CPB or with ECMO as we had only a small volume of counterparts. Furthermore, we have a unique public health insurance policy in Japan which rather generously covers expensive medical practice compared to other developed nations. The system resulted in substantially prolonged ICU or hospital stay in our cohort, which complicates the interpretation of the early outcomes. However, excellent survival outcomes strongly suggest that the thorough graft-protective reperfusion policy with CPB counteracts the adverse effects of ECD-LTx surgery.

In conclusion, the protective allograft reperfusion strategy using elective CPB achieved optimal outcomes after ECD-LTx, identical to SCD-LTx. Use of CPB does not significantly undermine survival of ECD-lung recipients if a careful total management for reperfusion is performed. CPB can offer excellent versatility and flexible surgical conditions. Thus, it is essential to continue to discuss not only whether CPB should be replaced by ECMO, but also how CPB should be used. Further multicenter studies to validate the use of intraoperative CPB in LTx are warranted.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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