Interactive CardioVascular and Thoracic Surgery 22 (2016) 314–320
doi:10.1093/icvts/ivv357 Advance Access publication 23 December 2015

ORIGINAL ARTICLE – THORACIC

Cite this article as: Mizota T, Miyao M, Yamada T, Sato M, Aoyama A, Chen F *et al*. Graft dysfunction immediately after reperfusion predicts short-term outcomes in living-donor lobar lung transplantation but not in cadaveric lung transplantation. Interact CardioVasc Thorac Surg 2016;22:314–20.

Graft dysfunction immediately after reperfusion predicts short-term outcomes in living-donor lobar lung transplantation but not in cadaveric lung transplantation

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Received 1 September 2015; received in revised form 28 October 2015; accepted 17 November 2015

Abstract

OBJECTIVES: Primary graft dysfunction (PGD) is a major cause of early morbidity and mortality after cadaveric lung transplantation (CLT). This study examined the incidence, time course and predictive value of PGD after living-donor lobar lung transplantation (LDLLT).

METHODS: We retrospectively investigated 75 patients (42 with LDLLT and 33 with CLT) who underwent lung transplantation from January 2008 to December 2013. Patients were assigned PGD grades at six time points, as defined by the International Society for Heart and Lung Transplantation: immediately after final reperfusion, upon arrival at the intensive care unit (ICU), and 12, 24, 48 and 72 h after ICU admission.

RESULTS: The incidence of severe (Grade 3) PGD at 48 or 72 h after ICU admission was similar for LDLLT and CLT patients (16.7 vs 12.1%; $P = 0.581$). The majority of the LDLLT patients having severe PGD first developed PGD immediately after reperfusion, whereas more than half of the CLT patients first developed severe PGD upon ICU arrival or later. In LDLLT patients, severe PGD immediately after reperfusion was significantly associated with fewer ventilator-free days during the first 28 postoperative days [median (interquartile range) of 0 (0–10) vs 21 (13–25) days, $P = 0.001$], prolonged postoperative ICU stay [median (interquartile range) of 20 (16–27) vs 12 (8–14) days, $P = 0.005$] and increased hospital mortality (27.3 vs 3.2%, $P = 0.02$). Severe PGD immediately after reperfusion was not associated with ventilator-free days during the first 28 postoperative days, time to discharge from ICU or hospital, or hospital mortality in CLT patients.

CONCLUSIONS: Postoperative incidence of severe PGD was not significantly different between LDLLT and CLT patients. In LDLLT patients, the onset of severe PGD tended to be earlier than that in CLT patients. Severe PGD immediately after reperfusion was a significant predictor of postoperative morbidity and mortality in LDLLT patients but not in CLT patients.

Keywords: Living-donor lobar lung transplantation • Cadaveric lung transplantation • Primary graft dysfunction • Reperfusion injury • Postoperative complications • Hospital mortality

INTRODUCTION

Living-donor lobar lung transplantation (LDLLT) was first performed in the 1990s in response to a mismatch between the supply and demand for donor lungs from brain-dead donors [1]. We recently demonstrated that survival following LDLLT is similar to that observed for cadaveric lung transplantation (CLT), despite the worse preoperative condition of LDLLT patients, and the use of LDLLT as a viable option in patients who may not survive a long waiting period for cadaveric donors [2]. In contrast, our analysis revealed that LDLLT patients require a greater duration of postoperative mechanical ventilation than CLT patients, probably due to the poorer preoperative condition of LDLLT patients. Early identification of patients with a poor postoperative course following LDLLT may help optimize postoperative management strategies, including the alteration of ventilation modalities or pharmacological agents [3–5].

Primary graft dysfunction (PGD), a form of acute lung injury occurring after lung transplantation [3, 6, 7], is known to significantly impact postoperative morbidity and mortality following lung transplantation. Severe PGD is associated with delayed extubation, prolonged stays in both intensive care and hospital, increased early mortality and worsened long-term outcomes in transplant survivors [6, 8–12]. In 2005, the International Society for Heart and Lung Transplantation (ISHLT) proposed a standardized definition of PGD [11], with subsequent studies validating this definition with data regarding clinical outcomes [13, 14]. However, each of these

studies involved CLT patients only. We previously reported severe PGD requiring extracorporeal membrane oxygenation (ECMO) in 4 of 14 LDLLT patients receiving grafts from a single donor [15]. However, the incidence of PGD after LDLLT according to ISHLT criteria is currently unknown, and the prognostic value of PGD in LDLLT has yet to be elucidated.

The purpose of this single-centre retrospective study was to examine the incidence and time course of PGD after LDLLT, and to assess the impact of PGD on outcomes in LDLLT patients.

MATERIALS AND METHODS

This retrospective cohort study was approved by the ethics committee of Kyoto University Hospital (approval number: E2080). All patients who underwent lung transplantation (LDLLT or CLT) at Kyoto University Hospital from 1 January 2008 to 31 December 2013 were eligible for this study. The medical records of eligible patients were reviewed with regard to patient characteristics, preoperative examination, and intra- and postoperative clinical course.

In Japan, all patients requiring CLT from brain-dead donors are registered at the Japan Organ Transplantation Network. The organ allocation process for CLT is largely based on the accrued time on the waiting list. The indications and size-matching criteria for LDLLT were described previously [2, 16]. Indication for LDLLT was limited to critically ill patients unlikely to survive waiting for cadaveric lungs. In LDLLT, graft forced vital capacity (FVC) was calculated using the following equation: (graft FVC) = (number of resected segments)/19. We accepted a size disparity when the graft FVC was 45% or more of the predicted FVC of the recipient (calculated according to height, age and gender).

Perioperative management was essentially identical for LDLLT and CLT patients. Although attending anaesthesiologists were responsible for ventilation during general anaesthesia, a positive end-expiratory pressure of 5 cmH_2O or greater was used following reperfusion in all cases. Postoperative respiratory management was performed according to a common protocol as previously described [17]. In brief, all patients were transferred to the intensive care unit (ICU) after lung transplantation, intubated and placed on artificial ventilation (Puritan Benett™ 840 Ventilator System: Covidien Japan, Tokyo, Japan) for at least 2 days postoperatively. From postoperative day 2, extubation was considered under the following circumstances: (i) stable vital signs with a Pa_{O_2}/FI_{O_2} ratio ≥200; (ii) stable underlying disease and complications; (iii) minimal artificial ventilation support; and (iv) sufficient spontaneous breathing. Tracheostomy was performed in all cases where prolonged artificial ventilation was necessary. Patients were considered for discharge from the ICU when haemodynamically stable, following extubation or tracheostomy.

Patients were assigned PGD grades at six time points according to the ISHLT definition of PGD: Immediately after final reperfusion (Trep), upon at ICU arrival (T0) and 12 h (T12), 24 h (T24), 48 h (T48) and 72 h (T72) after ICU admission (11). In brief, a Pa_{O_2}/FI_{O_2} ratio >300 was defined as Grade 0–1; a Pa_{O_2}/FI_{O_2} ≥200 and ≤0300 as Grade 2; and a Pa_{O_2}/FI_{O_2} <200 as Grade 3. Although the ISHLT PGD definitions divide patients with a Pa_{O_2}/FI_{O_2} >300 into two groups (Grade 0 and Grade 1) on the basis of the presence or absence of radiographic infiltrates, we classified any patient with a Pa_{O_2}/FI_{O_2} >300 as having Grade 0–1 PGD. Patients who were extubated were also classified as having Grade 0–1 PGD. Patients receiving ECMO were automatically classified as having Grade 3 PGD while receiving support.

When analysing the impact of PGD on outcomes, PGD Grades 0–1 and 2 were combined, and outcome measures were compared between patients with Grades 0–2 PGD and those with Grade 3 PGD. The primary outcome was defined as the number of days of unassisted breathing [ventilator-free days (VFDs)] during the initial 28 postoperative days. Patients who died or underwent retransplantation due to graft dysfunction during the initial 28 postoperative days were assigned 0 VFDs [18]. Unassisted breathing was defined as a period lasting at least 48 consecutive hours beginning with extubation (or removal of ventilatory support for patients with tracheostomies). Secondary outcomes included time to ICU and hospital discharge and hospital mortality.

Statistical analysis

Data were analysed using the statistical program R (http://cran.r-project.org). All data are presented as median (interquartile range) and number (percentage), unless stated otherwise. Differences between groups were compared using the Mann–Whitney *U*-test for continuous variables. For categorical variables, Pearson's χ^2-test or Fisher's exact test were used where appropriate. All statistical tests were two-tailed. Except for multivariate models, statistical significance was set at $P < 0.05$. Time-to-event analyses were used to compare lengths of ICU and hospital stays. Patient data were censored at the time of death or retransplantation. Medians and interquartile range were obtained using Kaplan–Meier analyses, and the log-rank test was used to assess differences between groups. Multivariate regression analysis was used to evaluate the independent role of Grade 3 PGD at Trep in predicting VFDs following LDLLT. All candidate covariates were included in multivariate analysis with a backward stepwise elimination performed to identify factors independently associated with VFDs. All variables maintaining a *P*-value <0.1 were included in the final model. Grade 3 PGD at Trep was included in all logistic models regardless of statistical significance as this was the primary variable of interest.

RESULTS

Patient characteristics and operative variables

A total of 75 lung transplantations (42 LDLLTs and 33 CLTs) were performed during the study period. Preoperative patient characteristics and operative variables are listed in Table 1. Although median ages were similar between LDLLT and CLT, 11 children under 15 years old underwent LDLLT, whereas no children underwent CLT. Dyspnoea, determined according to the Hugh-Jones classification, was significantly worse among LDLLT patients ($P = 0.005$), and the proportion of ventilator-dependent LDLLT patients tended to be higher (11.9 vs 3.0%, $P = 0.1597$). All patients required cardiopulmonary support during LDLLT; however, more than half (51.5%) of patients underwent CLT without cardiopulmonary support. The total ischaemic time was significantly shorter in LDLLT than that in CLT ($P < 0.0001$). A median graft FVC of 60.0% was observed in LDLLT patients and was found to be <55% in 15 patients (35.7%).

Prevalence and severity of primary graft dysfunction

The distribution of patients according to assigned PGD grades at six study time points is presented in Fig. 1. The incidence of at

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Table 1: Preoperative patient characteristics and operative variables

	LDLLT (n = 42)	CLT (n = 33)	P-value
Age (years)	44 (12–55)	40 (29–52)	0.873
Female gender	24 (57.1%)	12 (36.4%)	0.074
Body mass index (kg/m^2)	16.9 (14.0–19.7)	18.3 (16.6–21.5)	0.023
Hugh-Jones classification (III/IV/V)	1/18/23	2/25/6	0.005
Pre-existing lung disorder			0.001
Pulmonary fibrosis	20 (47.6%)	7 (21.2%)	
Bronchiolitis obliterans	13 (31.0%)	5 (15.2%)	
Pulmonary arterial hypertension	3 (7.1%)	2 (6.1%)	
Other	6 (14.3%)	19 (57.5%)	
Preoperative pulmonary hypertension	8 (19.0%)	3 (9.1%)	0.328
Preoperative condition			
NPPV	2 (4.8%)	0 (0.0%)	0.191
Ventilator-dependent	5 (11.9%)	1 (3.0%)	0.160
Type of transplant			0.001
Bilateral	33 (78.6%)	14 (42.4%)	
Single	9 (21.4%)	19 (57.6%)	
Use of cardiopulmonary support	42 (100.0%)	17 (51.5%)	<0.0001
Blood product volume administered intraoperatively (l)	5.7 (3.2–7.0)	2.6 (1.3–4.6)	0.001
Total ischaemic time (min)	154 (135–197)	452 (391–530)	<0.0001
Graft FVC (% of predicted FVC of the recipient)	60.0 (51.3–74.6)	–	–

Patients were considered to have pulmonary hypertension when the systolic pulmonary artery pressure (estimated by transthoracic echocardiography) was ≥60 mmHg.
LDLLT: living-donor lobar lung transplantation; CLT: cadaveric lung transplantation; NPPV: non-invasive positive pressure ventilation; FVC: forced vital capacity.

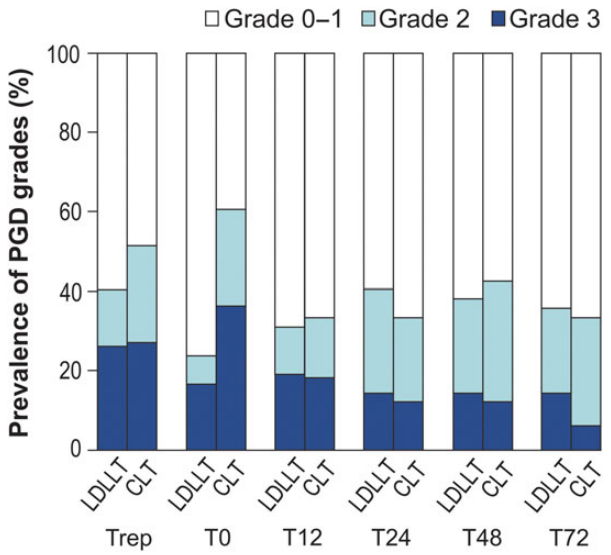

Figure 1: Prevalence and severity of PGD from immediately after reperfusion to 72 h after ICU admission. PGD: primary graft dysfunction; ICU: intensive care unit; CLT: cadaveric lung transplantation; LDLLT: living-donor lobar lung transplantation; Trep: immediately after final reperfusion; T0: at ICU arrival; T12–T72: 12–72 h after ICU admission.

least one period of Grade 3 PGD between Trep and T72 was 33.3% in LDLLT patients and tended to be lower than that in CLT patients (51.5%; P = 0.113). In LDLLT, 11 (26.2%) patients exhibited Grade 3 PGD at Trep with the incidence of Grade 3 PGD gradually decreasing thereafter. In CLT, 9 (27.2%) patients exhibited Grade 3 PGD at Trep, with the incidence of Grade 3 PGD highest at T0 (36.4%) and decreasing thereafter. The incidence of Grade 3 PGD at T48 or T72 was similar between LDLLT and CLT (16.7 vs 12.1%; P = 0.581) patients. Individual analyses at each time point revealed that the incidence of Grade 3 PGD was similar between LDLLT patients and CLT patients, except at T0, where the incidence of Grade 3 PGD tended to be higher in CLT patients than in LDLLT patients (36.4 vs 16.7%; P = 0.0645).

We further examined the timing of Grade 3 PGD onset. Among LDLLT patients, the majority of patients (72.7%) who experienced Grade 3 PGD developed Grade 3 PGD at Trep. Conversely, more than half (61.5%) of the CLT patients developed Grade 3 PGD at T0 or T12 (Fig. 2A). The presence of Grade 3 PGD at Trep was significantly associated with Grade 3 PGD at T48 or T72 in LDLLT patients (P < 0.0001); however, this association was not observed in CLT patients (P = 0.913; Fig. 2B and C).

Impact of Grade 3 primary graft dysfunction on ventilator-free days

Next, we investigated the impact of Grade 3 PGD at six study time points on VFDs during the initial 28 postoperative days (Table 2). Grade 3 PGD at all time points, including Trep, was strongly associated with decreased VFDs in LDLLT patients. In contrast, in CLT patients, Grade 3 PGD at Trep was not significantly associated with VFDs. Grade 3 PGD at T0 or later was significantly associated with VFDs in CLT patients, and the difference in median VFDs between Grades 0–2 and Grade 3 PGD was the greatest at T48 and T72. Six among 11 (54.6%) LDLLT patients with Grade 3 PGD at Trep had 0 VFDs; in contrast, 7 among 9 CLT patients (77.8%) with Grade 3 PGD at Trep successfully weaned off from ventilator support within 14 postoperative days. As the impact of Grade 3 PGD on VFDs was similar across time points in LDLLT patients, Grade 3 PGD at Trep was used in subsequent analyses.

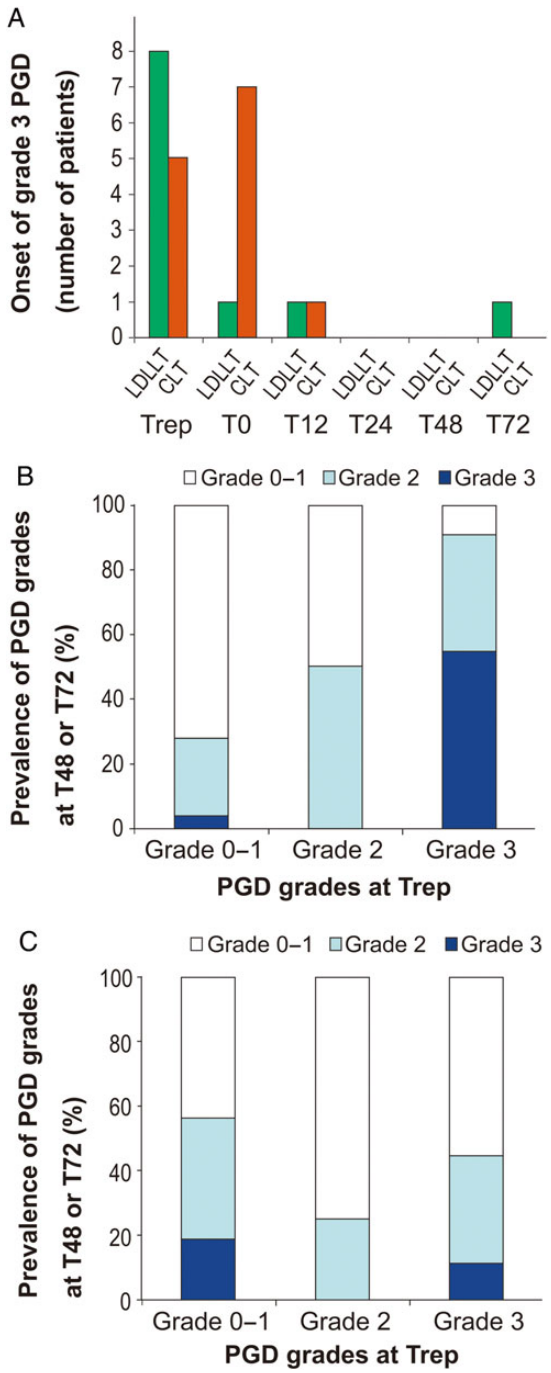

Figure 2: Time series analysis of PGD. (**A**) Timing of Grade 3 PGD onset; association between Grade 3 PGD at Trep and PGD grades at 48 or 72 h after ICU admission in living-donor lobar (**B**) and cadaveric (**C**) lung transplantation. PGD: primary graft dysfunction; ICU: intensive care unit; LDLLT: living-donor lobar lung transplantation; CLT: cadaveric lung transplantation; Trep: immediately after final reperfusion; T0: at ICU arrival; T12–T72: 12–72 h after ICU admission.

Impact of Grade 3 primary graft dysfunction on secondary outcome measures

We assessed the effect of Grade 3 PGD on the length of ICU and hospital stays and hospital mortality (Table 3). LDLLT patients with Grade 3 PGD at Trep had significantly longer stays in ICU than those without ($P = 0.005$). Moreover, hospital mortality was significantly higher in LDLLT patients with Grade 3 PGD at Trep than in those without. In contrast, Grade 3 PGD at Trep was not associated with duration of ICU or hospital stay, or hospital mortality, in CLT patients.

Multivariate analysis of ventilator-free days in patients with living-donor lobar lung transplantation

To determine the predictive value of Grade 3 PGD at Trep in LDLLT patients independently of pretransplant morbidity or transplant procedure type, multiple linear regression was performed, adjusting for the presence of pretransplant morbidity; specifically in age, body mass index, dyspnoea according to Hugh-Jones classifications (3–4 and 5), preoperative pulmonary hypertension, preoperative ventilator dependence; operative variables, specifically single-lung transplant, total donor graft ischaemic time and volume of intraoperatively administered blood products. Following backward elimination, variables that remained in the final model and that were found to be confounders were preoperative pulmonary hypertension, preoperative ventilator dependence and volume of intraoperatively administered blood products. Multivariate linear regression analysis revealed that Grade 3 PGD at Trep was significantly associated with decreased VFDs in LDLLT patients independently of pre- and intraoperative variables ($P = 0.01$; Table 4).

Characteristics associated with Grade 3 primary graft dysfunction at Trep in living-donor lobar lung transplantation

Finally, we assessed patient characteristics associated with the development of Grade 3 PGD at Trep in LDLLT patients (Table 5). Patients with Grade 3 PGD at Trep were significantly younger than those without ($P = 0.005$); of the 11 patients with Grade 3 PGD at Trep, 7 (63.6%) were children under 15 years old. Of note, six of nine single-lobe transplanted recipients developed Grade 3 PGD at Trep. The median graft FVC in the 7 children with PGD Grade 3 at Trep was 73.3% and five had a graft FVC of 55% or more. No significant association was observed between graft FVC and the development of Grade 3 PGD at Trep.

DISCUSSION

We investigated the incidence and time course of PGD following LDLLT and assessed the impact of Grade 3 PGD on outcomes in LDLLT patients. Analysis of our cohort revealed the following: (i) the incidence of Grade 3 PGD at 48 or 72 h after ICU admission was similar between LDLLT and CLT patients; (ii) the onset of Grade 3 PGD after LDLLT tended to be earlier than after CLT; and (iii) Grade 3 PGD at Trep was a significant predictor of fewer VFDs during the initial 28 postoperative days, prolonged postoperative ICU stay and increased hospital mortality in LDLLT patients.

Since the publication of the ISHLT standardized definition and grading of PGD, the incidence of Grade 3 PGD at 48 or 72 h after CLT has been reported to be between 10 and 20%, and the incidence rate of Grade 3 PGD at any time point during the initial 72 postoperative hours has been reported as ∼30% [19]. The incidence of Grade 3 PGD after LDLLT observed in our study (33.3% at

Table 2: Impact of severe PGD at each time point on VFDs

	Trep	T0	T12	T24	T48	T72
LDLLT						
Grade 0–2	21 (13–25)	21 (10–25)	22 (9–25)	21 (6–25)	21 (6–25)	21 (6–25)
Grade 3	0 (0–10)	0 (0–7)	0 (0–9)	0 (0–8)	0 (0–8)	0 (0–10)
P	0.001	0.002	0.002	0.004	0.004	0.007
CLT						
Grade 0–2	24 (17–26)	25 (18–26)	25 (18–26)	24 (18–26)	24 (18–26)	24 (17–25)
Grade 3	18 (8–25)	18 (7–24)	6 (0–17)	14 (4–18)	3 (0–15)	3 (0–5)
P	0.245	0.029	0.001	0.030	0.008	0.030

PGD: primary graft dysfunction; VFDs: ventilator-free days; Trep: immediately after reperfusion; T0: at ICU arrival; T12–T72, 12–72 h after ICU admission; LDLLT: living-donor lobar lung transplantation; CLT: cadaveric lung transplantation.

Table 3: Impact of Grade 3 PGD at Trep on outcomes according to transplantation procedure

	Grade 3 PGD at Trep (*n* = 11)	Grade 0–2 PGD at Trep (*n* = 31)	*P*-value
LDLLT			
Time to discharge (days)			
From ICU	20 (16–27)	12 (8–14)	0.005
From hospital	99 (60–114)	81 (58–91)	0.093
Hospital mortality	3 (27.3%)	1 (3.2%)	0.020
	Grade 3 PGD at Trep (*n* = 9)	Grade 0–2 PGD at Trep (*n* = 24)	*P*-value
CLT			
Time to discharge (days)			
From ICU	9 (7–13)	7 (5–11)	0.741
From hospital	46 (43–76)	53 (43–90)	0.971
Hospital mortality	1 (11.1%)	1 (4.2%)	0.457

PGD: primary graft dysfunction; at Trep: immediately after reperfusion; LDLLT: living-donor lobar lung transplantation; CLT: cadaveric lung transplantation; ICU: intensive care unit.

Table 4: Multivariate linear regression analysis of VFDs during the initial 28 postoperative days in LDLLT patients

Variables	Regression coefficient	95% CI	*P*-value
Grade 3 PGD at Trep	−8.48	−14.82 to −2.13	0.010
Ventilator-dependent	−13.27	−22.09 to −4.46	0.004
Preoperative pulmonary hypertension	−5.72	−12.25 to 0.81	0.084
Blood volume administered intraoperatively (l)	−0.83	−1.59 to −0.06	0.035

VFDs: ventilator-free days; LDLLT: living-donor lobar lung transplantation; PGD: primary graft dysfunction; at Trep: immediately after reperfusion; CI: confidence interval.

any time point from Trep to T72 and 16.7% at T48 or T72) was not found to significantly differ from those after CLT and was similar to previously reported incidences in CLT. However, the time course of PGD significantly differed between LDLLT and CLT patients. In CLT, more than half of patients with Grade 3 PGD first developed Grade 3 PGD at T0 or T12, corroborating a previous study that reported a significant variation in the Pa_{O_2}/FI_{O_2} ratio within the first 12 postoperative hours with stabilization thereafter [20]. In contrast, the majority of patients developing Grade 3 PGD following LDLLT developed Grade 3 PGD at Trep, with a few patients found to develop Grade 3 PGD at T0 or later.

The difference in the time course of PGD between LDLLT and CLT patients might be explained by differing mechanisms underlying the development of PGD in these patient populations. PGD is characterized by pulmonary oedema with diffuse alveolar damage associated with ischaemia and reperfusion of lung grafts [3, 11]. Factors thought to contribute to the injury of lung grafts from cadaveric donors during brain death or prolonged

Table 5: Characteristics associated with Grade 3 PGD at Trep among LDLLT patients

	Grade 0–2 PGD at Trep (n = 31)	Grade 3 PGD at Trep (n = 11)	P-value
Age (years)	49 (22–57)	11 (6–41)	0.005
Child (<15 years old)	4 (12.9%)	7 (63.6%)	0.001
Single-lobe transplantation	3 (9.7%)	6 (54.6%)	0.002
Blood product volume administered intraoperatively (l)	6.0 (3.2–7.3)	5.2 (1.6–7.0)	0.501
Total ischaemic time (min)	159 (141–193)	111 (88–204)	0.179
Graft FVC (% of predicted FVC of the recipient)	58.1 (52.7–69.3)	67.0 (49.1–79.3)	0.699
Graft FVC <55%	11 (35.5%)	4 (36.4%)	0.958

PGD: primary graft dysfunction; at Trep: immediately after reperfusion; LDLLT: living-donor lobar lung transplantation; FVC: forced vital capacity.

mechanical ventilation include pneumonia, aspiration, blood transfusion, haemodynamic instability and ventilation-associated injury. Moreover, graft ischaemic time is much greater in CLT patients than in LDLLT patients. We therefore propose that patients who underwent CLT were at higher risk of severe ischaemia–reperfusion injury. In contrast, grafts from LDLLT donors are not exposed to infection or mechanical ventilation and have a shorter ischaemic time. We discussed the concept of 'a small but perfect graft' previously [2], and size mismatch has been shown to be the predominant cause of graft dysfunction in LDLLT [15]. The results of this study may suggest that graft dysfunction due to size mismatch can be assessed at Trep, whereas graft dysfunction due to ischaemia–reperfusion injury cannot be assessed until development of dysfunction at later time points.

Appropriate size matching between donors and recipients is crucial in LDLLT. The use of a graft too small for a recipient may result in poor ventilation (functional size matching), and the use of a graft too large for the recipient hemithorax may result in high airway resistance, atelectasis and haemodynamic instability at chest closure (anatomical size matching) [15]. As is presented in Table 5, paediatric patients receiving single-lobe transplantation were apparently at greater risk of developing severe PGD. This finding corroborates our previous report [15] suggesting that bilateral LDLLT is a better option when two living donors are available.

Our study revealed that Grade 3 PGD at Trep is a useful prognostic marker following LDLLT. As PGD grades at very early time points predict lung transplant outcomes, measurement of this parameter may allow earlier intervention in a specific group of patients. In contrast, Grade 3 PGD at Trep was not found to be a significant prognostic marker following CLT. As the Pa_{O_2}/FI_{O_2} ratio dynamically changes during the early post-transplant period in CLT, the use of later time points may be more appropriate for the assessment of graft function. Previous studies have demonstrated that Grade 3 PGD at T48–T72 has construct validity for determining long-term outcomes and concurrent lung injury markers [14, 21]; therefore, the assessment of PGD on postoperative day 2 or 3 may have greater utility.

In the multivariate analysis of VFDs in LDLLT patients, preoperative mechanical ventilation, preoperative pulmonary hypertension and the volume of intraoperatively administered blood products remained in the final model. Each of these factors has been implicated as a predictive factor in previous studies of lung transplant outcomes in CLT patients [22–25]. These may represent prognostic factors common to both LDLLT and CLT.

The major limitations of this study were its retrospective design and small sample size. Data collected in this study were derived from a single institution. Heterogeneity in procedures (e.g. single and bilateral lung transplantation) and pretransplant status made it difficult to interpret the results; future studies are warranted to confirm our results by taking these variables into account. Ventilator settings potentially influenced Pa_{O_2}/FI_{O_2}. Despite these limitations, our data provide new information regarding the postoperative respiratory management of LDLLT patients.

In conclusion, this study found that the incidence of severe (Grade 3) PGD after LDLLT did not significantly differ from the incidence of severe PGD following CLT. In LDLLT patients, the onset of severe PGD tended to be earlier than that in CLT patients. Severe PGD at Trep was a significant predictor of fewer VFDs, a longer postoperative ICU stay and increased hospital mortality in LDLLT patients.

ACKNOWLEDGEMENTS

The authors thank Enago (www.enago.jp) for the English language review.

Conflict of interest: none declared.

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eComment. Lung size mismatch and graft dysfunction immediately after reperfusion

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doi: 10.1093/icvts/ivw026

We read with great interest the manuscript by Mizota *et al.* describing the incidence and timing of primary graft dysfunction (PGD) in living donor lobar lung transplantation (LDLLT) and comparing this to cadaveric lung transplantation (CLT) [1]. The authors found that in LDLLT patients, the onset of severe PGD tended to be earlier and that severe PGD immediately after reperfusion was a significant predictor of postoperative morbidity and mortality.

Donor-to-recipient lung size mismatch in LDLLT is a common occurrence. We have conducted a series of investigations on the associations between donor-to-recipient lung size mismatch and outcomes after lung transplantation in CLT-recipients and have found the following:

(a) Undersizing (as assessed by the donor-to-recipient predicted total lung capacity ratio [pTLCratio]) is an independent risk factor for PGD in bilateral CLT [2];
(b) In a study of bilateral CLT, tidal volumes during mechanical ventilation (when tidal volumes were indexed to donor predicted body weight, as an estimate of the actual size of the allograft), were substantially higher (and potentially injurious), if the allograft was undersized compared to oversized allografts [2,3];
(c) Undersizing is an independent predictor of one-year mortality following CLT [4].

In the study by Mizota *et al.*, lung size matching was assessed by calculating graft forced vital capacity. The majority of patients undergoing LDLLT with grade 3 PGD at reperfusion had a single-lung lobar transplant (55%) and were <15 years old (64%) [1]. The authors reported that there was no association between graft forced vital capacity and the development of grade 3 PGD at reperfusion in LDLLT. However, it is not clear how the authors accounted for the impact of single-lung LDLLT and paediatric age in their assessment of lung size mismatch. It would be helpful, if the authors could provide pTLCratio data (actual donor pTLC transplanted via lobar transplant/pTLC of the recipient) and the association between pTLCratio and PGD.

A consequence of ischaemia reperfusion injury is endothelial cell leak. Pulmonary oedema formation following reperfusion from this mechanism is transient and most apparent in the first 5–15 minutes of reperfusion. If an allograft is undersized below a critical threshold regarding the size of the pulmonary vascular bed, it is possible that this could lead to pulmonary oedema formation immediately following reperfusion. To avoid this, either a larger vascular surface area (larger allograft) would need to be transplanted, or an intra- and postoperative strategy that uses extracorporeal support to unload the undersized allograft would be needed, until the endothelial cell leak is resolved.

Furthermore, we recommend lung protective mechanical ventilation with low tidal volumes (6 ml/kg predicted body weight) and positive end expiratory pressure for the post-lung transplant period. In our opinion, the tidal volume needs to be based on donor-characteristics (donor predicted body weight, as a parameter of actual allograft size), rather than based on recipient characteristics to avoid potentially injurious ventilator settings for the recipients of undersized allografts [5].

Conflict of interest: none declared.

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