Improved survival after living-donor lobar lung transplantation

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Shimizu and Date

Objective: Survival after living-donor lobar lung transplantation has been reported to be similar to that after cadaveric lung transplantation. The purpose of this study was to summarize our 5-year experience of living-donor lobar lung transplantation for critically ill patients.

Methods: Between October 1998 and April 2004, we performed living-donor lobar lung transplantation in 30 critically ill patients with various lung diseases, including 5 (17%) patients on a ventilator. Mean age was 30.4 years (range, 8-55 years). Postoperative management included slow weaning from a ventilator, relatively low-dose immunosuppressants, and careful rejection monitoring on the basis of radiographic and clinical findings without transbronchial lung biopsy.

Results: The average duration of mechanical ventilation was 15.4 days, intensive care unit stay was 23.5 days, and hospital stay was 64.6 days. Clinically judged acute rejection occurred at an average rate of 1.5 episodes per patient, but infection occurred in only one patient during the first month. In spite of the complicated postoperative course, all patients were discharged without oxygen inhalation. Four patients had unilateral bronchiolitis obliterans syndrome, but the decrease in their forced expiratory volume in 1 second values stopped within 9 months. All 30 recipients are currently alive, with a follow-up period of 1 to 66 months. All donors have returned to their previous lifestyles.

Conclusions: Living-donor lobar lung transplantation can be applied to both pediatric and adult patients with very limited life expectancies. It might provide better survival than conventional cadaveric lung transplantation.

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Read at the Eighty-fourth Annual Meeting of The American Association for Thoracic Surgery, Toronto, Ontario, Canada, April 25-28, 2004.

Received for publication April 17, 2004; revisions received July 19, 2004; accepted for publication July 23, 2004.

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J Thorac Cardiovasc Surg 2004;128:933-40

0022-5223/$30.00

doi:10.1016/j.jtcvs.2004.07.032

Lung transplantation has been performed internationally as an effective treatment for a variety of end-stage lung diseases. A great disparity between the supply of donor organs and the demand of potential recipients has resulted in longer waiting times and annual increases in deaths on the lung transplant waiting list. As a consequence, efforts have been directed toward the use of marginal donors,[1,2] non–heart-beating donors,[3] and living donors.[4-8]

Bilateral living-donor lobar lung transplantation (LDLLT) was clinically developed at the University of Southern California as a procedure for patients considered

TABLE 1. Okayama University triple-drug immunosuppressive protocol for living-donor lobar lung transplantation

Cyclosporine			
Before transplantation	None		
After transplantation	Dosage adjusted to maintain trough level at:		
	3 mo after transplantion		250-350 ng/mL
	6 mo after transplantion		200-300 ng/mL
	12 mo after transplantion		150-250 ng/mL
Tacrolimus			
Before transplantation	None		
After transplantation	Dosage adjusted to maintain trough level at:		
	3 mo after transplantion		10-20 ng/mL
	6 mo after transplantion		10-15 ng/mL
	12 mo after transplantion		8-12 ng/mL
Azathioprine			
Before transplantation	2 mg/kg		
After transplantation	2 mg/kg per d		
Mycophenolate mofetil			
Before transplantation	500 mg		
After transplantation	500-1000 mg twice daily		
Corticosteroids			
Before reperfusion		Methylprednisolone (iv)	500-1000 mg
After transplantation	3 d after transplantion	Methylprednisolone (iv)	125 mg per d
	6 mo after transplantion	Prednisone (oral)	0.4 mg/kg per d
	12 mo after transplantion	Prednisone (oral)	0.2 mg/kg per 2 d

iv, Intravenous.

too ill to await cadaveric transplantation.[4-6] In the recent report from this group, the overall actuarial survival of 123 LDLLT recipients was 45% at 5 years.[7]

Stimulated by their pioneering work, we began a program of LDLLT at Okayama University Hospital in October 1998.[8] The purpose of this study was to summarize our 5-year experience in LDLLT for 30 consecutive patients with limited life expectancy.

Methods

Patient and Donor Selection

All recipients fulfilled the criteria for conventional bilateral lung transplantation. We have accepted only critically ill patients as candidates for LDLLT and only relatives within the second degree or a spouse as living donors. Each case was carefully reviewed by the Lung Transplant Evaluation Committee at Okayama University Hospital. Regarding the size matching, we have previously proposed a formula to estimate the graft forced vital capacity (FVC) on the basis of the donor's measured FVC and the number of pulmonary segments implanted.[8] When the total FVC of the 2 grafts was more than 50% of the predicted FVC of the recipient, we accepted the size disparity, regardless of the recipient's diagnosis.

Operative Technique

The surgical aspects of LDLLT have been previously described in detail.[4,9] The right and left lower lobes were removed from 2 healthy donors. On the back table, the lobes were flushed with 1 L of Euro-Collins solution both antegradely and retrogradely from a bag about 50 cm above the table. Then these 2 lobes were implanted in the recipient as whole right and left lungs during cardiopulmonary bypass. The bronchial wrapping with local fat tissue was performed in patients receiving high-dose steroid therapy. Just before reperfusion, 500 mg to 1 g of methylprednisolone was administered intravenously, and nitric oxide inhalation was initiated at 20 ppm. At the conclusion of the operation, a nasal feeding tube was inserted to the proximal jejunum under the fluoroscope.

Postoperative Management of the Recipient

The patient was kept intubated for at least 3 days to maintain optimal expansion of the lobes. Weaning from a ventilator was intentionally slow, and tracheostomy was performed when patients showed any signs of sputum retention. Fiberoptic bronchoscopy was performed every 12 hours during intubation to suction any retained secretions. An intensive program of chest physiotherapy was given every 4 hours. The choice of antibiotics was based on the results of daily sputum culture. Cytomegalovirus prophylaxis with ganciclovir was given to all recipients for the first 3 months. Postoperative immunosuppression consisted of triple-drug therapy with cyclosporine (INN: ciclosporin) or tacrolimus, azathioprine, or mycophenolate mofetil (MMF) and corticosteroids (Table 1). Induction cytolytic therapy was not used. The combination of cyclosporine, azathioprine, and steroid was chosen for patients with infectious lung diseases, pediatric patients, and patients already receiving steroids; the combination of tacrolimus, MMF, and steroid was used for other patients. Except for 125 mg of methylprednisolone during the first 3 days, all immunosuppressants were administered through the nasal tube inserted in the proximal

TABLE 2. Diagnoses for living-donor lobar lung transplantation

Diagnoses	No.
Primary pulmonary hypertension	10
Idiopathic interstitial pneumonia	7
Bronchiolitis obliterans	5
Bronchiectasis	3
Lymphangioleiomyomatosis	2
Cystic fibrosis	1
Eisenmenger syndrome	1
Multiple bullae	1
Total	30

TABLE 3. Preoperative condition of recipients (n = 30)

Preoperative condition	No.
Oxygen dependent	30 (100%)
Hospital bound	26 (87%)
Bed bound	22 (73%)
Body mass index <17	17 (57%)
Steroid dependent	15 (50%)
ICU management	13 (43%)
Previous thoracotomy	9 (30%)
Ventilator dependent	5 (17%)

jejunum. Under careful monitoring of daily serum creatinine levels and creatinine clearance, cyclosporine and tacrolimus trough levels were often reduced to less than the target range. The immunosuppressant protocol was the same as for our cadaveric program.

We judged acute rejection on the basis of radiographic and clinical findings without transbronchial lung biopsy. Early acute rejection episodes were characterized by dyspnea, low-grade fever, leukocytosis, hypoxemia, and diffuse interstitial infiltrate on chest radiographs. A trial bolus dose of 500 mg of methylprednisolone was administered, and various clinical signs were carefully observed. If acute rejection was indeed the problem, 2 additional daily bolus doses of methylprednisolone were given. If acute rejection was encountered more than 3 times, cyclosporine plus azathioprine was switched to tacrolimus plus MMF. When all these treatments failed, OKT3 was used.

Long-Term Follow-up of the Recipient

Three months after LDLLT, patients were allowed to return to their home town. They were asked to keep a diary that included daily pulmonary function, digital saturation, body temperature, body weight, blood pressure, and heart rate. The diary was sent to a lung transplant coordinator every month. Routine full postoperative assessment was performed at 6 months, 12 months, and then annually.

Results

We performed LDLLT in 30 patients from October 1998 through April 2004. There were 25 female and 5 male patients, with ages ranging from 8 to 55 years (average, 30.4 years). Six of the patients were children, and 24 were adults. The recipients' diagnoses are listed in Table 2. All 10 patients with primary pulmonary hypertension were receiving high-dose intravenous epoprostenol (average, 89.0 ng · kg^{-1} · min^{-1}). In 5 patients with bronchiolitis obliterans syndrome (BOS), 3 were after bone marrow transplantation for leukemia (n = 2) and aplastic anemia (n = 1), 1 was after Steven-Johnson syndrome,[10] and 1 was caused by ingestion of *Sauropus androgynus*.[11]

The preoperative condition of the 30 recipients is summarized in Table 3. We have accepted patients dependent on high-dose (as high as 50 mg/d prednisone) systemic corticosteroid therapy. Five (17%) patients were on a ventilator at the time of transplantation for as long as 7 weeks (21.2 ± 4.2 days; range, 14-36 days).

Bilateral LDLLT was performed in 29 patients, and right single LDLLT was performed for a 10-year-old boy with primary pulmonary hypertension[12] because his mother was the only available donor.

Among the 59 living donors, 5 were non-blood-related donors (patients' husbands), and others were blood-related donors within the second degree. The total FVC of the 2 grafts was estimated to range from 51.4% to 103.0% (average, 67.1%) of the predicted FVC of the recipient. Sixteen (53%) patients received an ABO-identical LDLLT, and 14 (47%) patients received an ABO-compatible LDLLT with a minor ABO mismatch.

Regarding immunosuppressants, the combination of cyclosporine, azathioprine, and steroid was chosen for 21 (70%) patients, and the combination of tacrolimus, MMF, and steroid was chosen for 9 (30%) patients. During the first month, clinically judged acute rejection occurred at an average rate of 1.5 ± 0.2 episodes per patient. Cyclosporine plus azathioprine was switched to tacrolimus plus MMF in 4 patients as a result of repeated episodes of acute rejection. OKT3 was used in 3 patients. Under careful monitoring of daily serum creatinine levels and creatinine clearance, cyclosporine and tacrolimus trough levels were often reduced to less than the target range. The trough level of cyclosporine was maintained at less than 250 ng/mL, and that of tacrolimus was maintained at less than 15 ng/mL during the first 2 weeks (Figure 1). Except for one patient in whom transient cytomegalovirus enteritis developed, no patient had infectious complications. There were no bronchial complications in the 59 bronchial anastomoses.

The most frequent complication was lung edema, which occurred in 6 (20%) patients. Other major complications included transient peroneal nerve palsy (n = 3), renal dysfunction (n = 3), hemorrhage necessitating rethoracotomy (n = 2), cardiac tamponade (n = 2), kinking of the pulmonary artery (n = 2), hemolytic anemia (n = 2), transient

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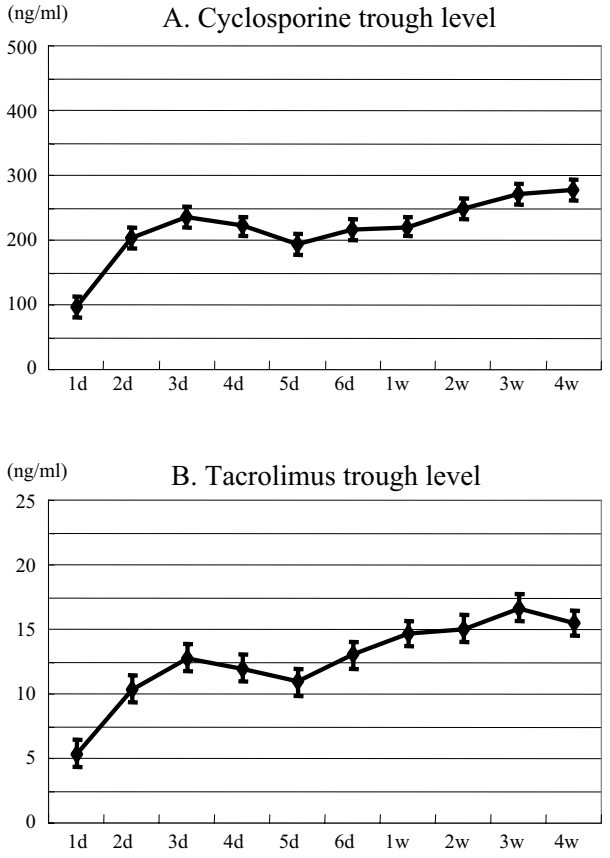

Figure 1. A, Cyclosporine trough level during the first month after LDLLT (n = 21). B, Tacrolimus trough level during the first month after LDLLT (n = 9).

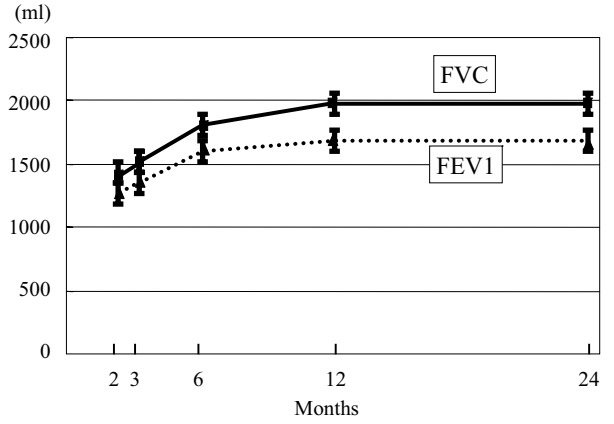

Figure 2. Changes in FVC and FEV_1 after LDLLT.

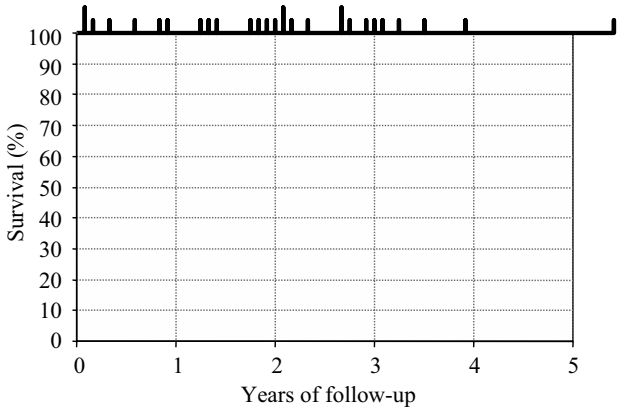

Figure 3. Survival of 30 recipients after LDLLT.

phrenic nerve palsy (n = 2), and massive hemoptysis (n = 1). Tracheostomy was required in 15 (50%) patients, reintubation in 7 (23%) patients, rethoracotomy in 3 (10%) patients, continuous hemodiafiltration in 3 (10%) patients, and extracorporeal membrane oxygenation in 1 (3%) patient. The duration of mechanical ventilation required was 15.4 ± 2.8 days, and intensive care unit stay was 23.5 ± 2.9 days. Despite the complicated postoperative course, all 30 patients were discharged without oxygen inhalation after an average hospital stay of 64.7 ± 4.2 days. Although their FVC (1396 ± 57 mL, 51.0% of predicted value) was limited at discharge, arterial oxygen tension on room air (94.2 ± 1.8 mm Hg) and systolic pulmonary artery pressure (24.5 ± 1.2 mm Hg) were excellent.

FVC improved gradually after discharge and reached 1974 ± 87 mL (71.8% of predicted value) at 1 year (Figure 2). The improvement in FVC was associated with the improvement in forced expiratory volume in 1 second (FEV_1), indicating that there was no obstructive change in the transplanted grafts.

Over the course of this study, 4 patients (16% of 3-month survivors) had unilateral BOS at 11, 12, 17, and 42 months after LDLLT, respectively. The contralateral graft was unaffected in these 4 patients, and their FEV_1 decrease stopped within 9 months.

At the time of final data analysis on April 18, 2004, the mean time from transplantation to final analysis for the 30 patients was 22.2 months, ranging from 1 to 66 months. There has been no mortality during the observation period (Figure 3).

Discussion

The current availability of cadaveric donor lungs has not been able to meet the increasing demand of potential recipients. As a consequence, efforts have been directed toward the use of marginal donors,[1,2] non–heart-beating donors,[3] and living donors.[4-8] Bilateral LDLLT was applied at the University of Southern California (USC) in the early 1990s as an alternative to cadaveric lung transplantation.[4-6] In a recent report on 123 patients receiving LDLLT, the primary indication for transplantation was cystic fibrosis (84%).[7] Despite the critical condition of many of these patients, the

overall actuarial survivals of 70%, 54%, and 45% at 1, 3, and 5 years, respectively, were comparable with those of reported bilateral cadaveric lung transplantation from the International Society for Heart and Lung Transplant registry.[13]

Encouraged by this work, we applied this procedure to both pediatric and adult patients in 1998. We recently reported our early results with this procedure in a cohort of 4 pediatric and 10 adult patients. All 14 patients were alive, with the longest follow-up period of 45 months. We now have accumulated our experience of LDLLT in 30 patients, with the longest follow-up period of 66 months.

The optimal immunosuppressive treatment remains unknown. Our approach to LDLLT recipients focuses on moderating calcineurin inhibitor levels during the first 2 weeks in the hope of decreasing the risk of infection to protect renal function and thereby to decrease the risk of lung edema. Although the target range was 250 to 350 ng/mL for cyclosporine and 10 to 20 ng/mL for tacrolimus, the trough level was maintained at less than 250 ng/mL for cyclosporine and 15 ng/mL for tacrolimus, respectively, during the first 2 weeks, as shown in Figure 1. As a result, no life-threatening infection was encountered among the 30 recipients. The average serum creatinine level remained normal (0.66 ± 0.99 mg/dL) 2 weeks after LDLLT. We avoided intravenous administration of immunosuppressants by using a feeding tube inserted into the proximal jejunum. Enteral administration of immunosuppressants appeared to be less toxic to renal function. The feeding tube was also useful for nutritional support in the early postoperative period.

The high incidence of acute rejection, 1.5 ± 0.2 episodes per patient, might be related to the relatively low immunosuppression or to the method of detecting acute rejection. Transbronchial lung biopsy offers a safe and accurate means of diagnosis of acute rejection after cadaveric lung transplantation and has emerged as the procedure of choice.[14] However, the risk of pneumothorax and bleeding after transbronchial lung biopsy might be greater after LDLLT because the small grafts are receiving the entire cardiac output with undetectable dead space. Thus we judged acute rejection on the basis of radiographic and clinical findings.

There are several important concepts in the respiratory management of LDLLT recipients because of the small size of the implanted lungs. We wean the patients from a ventilator very slowly so that the small lobes can maintain optimal expansion. FVC measured immediately before extubation was only about 500 mL in general. If the patients show any sign of sputum retention, we reintubate and perform a tracheostomy without hesitation. The average duration of mechanical ventilator use was more than 2 weeks, and tracheostomy was required for half of the recipients. It should also be noted that the early tracheostomy made it possible to wean the recipients from the ventilator very slowly. Frequent use of a fiberoptic bronchoscope and an intensive program of chest physiotherapy appeared to be important in decreasing the risk of infection. Because a limited amount of vascular bed was implanted in LDLLT, nitric oxide inhalation was routinely used to decrease the risk of pulmonary hypertension and lung edema.

The history of lung transplantation in Japan is short because of society's difficulty in accepting the concept of brain death. The transplant law was finally passed, and the first successful cadaveric lung transplantation was performed in March 2000. We could perform only 4 cadaveric lung transplantations in our institution compared with 30 LDLLTs because of the scarcity of available cadaveric donors. However, we have accepted only critically ill patients for LDLLT because of the possible serious morbidity associated with donor lobectomy.[15] The preoperative condition of the 30 LDLLT recipients was very poor, as summarized in Table 3. Most of the patients (73%) were bed bound, and 5 (17%) were supported by ventilators. The USC group recently reported that patients on ventilators preoperatively had significantly worse outcomes.[7]

In our series the reasons for transplantation have included hypertensive (n = 11, 37%), obstructive (n = 8, 27%), restrictive (n = 7, 23%), and infectious (n = 4, 13%) lung diseases.

Because cystic fibrosis is rare in Japan, it was the indication in only 1 (3%) patient compared with in 84% of the patients in the USC series.[7] Of note, infection was the predominant cause of death (53%) in their report.

BOS has been the major obstacle after lung transplantation.[13,16,17] The question remains of whether patients receiving LDLLT will have less BOS than those receiving conventional cadaveric lung transplantation. Starnes and colleagues[18] reported that LDLLT recipients had less BOS than cadaveric lung transplant recipients in the pediatric population. Interestingly, all 4 patients with BOS in our study had unilateral BOS, and their FEV_1 decrease stopped within 9 months. The different antigenicity between 2 LDLLT grafts might explain this phenomenon.

Despite poor preoperative condition and complicated early postoperative course, all recipients were sent home without the need for oxygen inhalation. Their quality of life was excellent, along with the improvement in pulmonary function. Although our experience with LDLLT is still limited in terms of both numbers (n = 30) and observation period (1-66 months), 100% survival during the observation period is noteworthy. We believe that enteral administration of low-dose immunosuppressants,

careful rejection monitoring without transbronchial lung biopsy, and slow weaning from a ventilator were effective strategies for LDLLT during the early postoperative period. The 2 lobes obtained from 2 different donors appear to be beneficial in the long term because contralateral unaffected lung might act as a reservoir in the case of unilateral BOS. We conclude that LDLLT might provide better survival than conventional cadaveric lung transplantation.

We acknowledge the excellent advice on our patient care obtained from Elbert P. Trulock, MD (Washington University School of Medicine), and Mark L Barr, MD (University of Southern California).

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Discussion

Dr John C. Wain, Jr (*Boston, Mass*). Dr Date, congratulations to you. It is really a remarkable series with that survival in those patients. The experience is remarkable not only because of the survival, but I think your recipient population is unique in terms of the high incidence of pulmonary hypertension. Most of the patients, of course, have nonseptic lung disease. In addition, in the manuscript you mentioned that all patients received inhaled nitric oxide as part of their perioperative management, which is certainly somewhat novel. The empiric diagnosis, if you will, of acute rejection at first sounds unique, but, as I thought about it, most of the time you make the diagnosis on clinical grounds anyway. I think you are to be commended for emphasizing that point as well. On the other hand, the lack of late graft dysfunction from BOS is really quite remarkable, as is the fact that, as you pointed out in your presentation, it appears to stabilize in the unilateral sense after a period of time.I have several questions about all of this, and I hope to gain some insights in managing our own patients. First, you contend that the postoperative ventilation with low lung volumes contributes to your improved outcomes, and well it might. Certainly there is a large body of literature that suggests that overdistension of the lung leads to concomitant lung injury. However, in our own experience with 15 of these patients, we have observed that lung injury often is manifested immediately after reperfusion, right in the operating room. I was wondering, with regard to that and the subsequent postoperative ventilation, whether you have any specific algorithm for reinflation and reperfusion of the lung grafts in the operating room.

Dr Date. At the time of reperfusion, we try to make sure there is no atelectasis left in the small grafts transplanted. Because of the small grafts we transplanted, if you have a small amount of atelectasis, your Po_2 will be very low. Therefore, we make sure that the lung is well expanded.

Dr Wain. What sort of inflation pressures do you use both in the operating room and then postoperatively?

Dr Date. The maximal ventilation pressure should be less than 20 mm Hg. Therefore, our tidal volume is usually around 200 to 250, very small.

Dr Wain. Are you managing patients with volume ventilation or pressure-limited ventilation? How do you do that?

Dr Date. Our intensive care unit staffs handle that, so I do not know. I am sorry.

Dr Wain. That's fine. In terms of the nitric oxide, is that started in the operating room, or when is that initiated?

Dr Date. The first ventilation going into the transplanted lung contains nitric oxide.

Dr Wain. With regard to the rejection issues, do you have any MHC data on these patients to look at? For instance, do the patients who have acute rejection have more than one episode or

do they have many episodes, and can you relate that to the MHC matching?

Dr Date. As I said, our acute rejection was just based on clinical and radiographic findings. Therefore, only 40% of the patients had radiographically evident acute rejection, and usually those are only unilateral lung. There is also good information to differentiate it between rejection and infection in this particular group of patients.

Dr Wain. With regard to the acute rejection, was there any difference in the unrelated versus the related donors?

Dr Date. Thus far, no.

Dr Wain. In regard to the unilaterality of it, was there a preponderance of that on the right side with reference to the possibility of reflux and aspiration?

Dr Date. There was no difference between the right side and the left side.

Dr Wain. Last, what is your conjecture about the long-term BOS or lack thereof in these patients? Is it because of a short ischemic interval on the donor side? Is it because of less lung inflammation up front? Is it because of the nitric oxide?

Dr Date. We do not know. Still, we are not sure whether LDLLT will have a lower incidence of BOS compared with cadaveric lung transplantation. I think the follow-up period is too short to make a final conclusion.

Dr Wain. The cadaveric transplantations that you do, do you manage them in the same way in terms of limiting ventilation and nitric oxide and so on?

Dr Date. Basically, yes. Because we get used to handling it this way, it is easier for us to handle it in the same way for cadaveric lung transplantation as well.

Dr Wain. Right. Stick with the system. Well, it obviously works, and congratulations.

Dr Erino A. Rendina (*Rome, Italy*). First of all, congratulations, Dr Date. These results are really impressive.

I would like you to comment on one issue. You say in your abstract that you use relatively low-dose immunosuppressants, and yet, according to that, you have reported no infection in the early postoperative period in your patients. Therefore, you seem to favor control of infection over vigorous early immunosuppression. Do you want to comment on what the destiny in terms of the risk of BOS will be for these patients?

Dr Date. Erino, that is an excellent question. We believe that preventing infection is more important than preventing acute rejection in the early period because acute rejection rarely is the cause of death in the early period. However, the average rate of acute rejection per patient is 1.5, which seems to be higher than in the other report, and we are not sure whether that will correlate with the higher incidence of BOS in the future. Time will tell.

Dr Bryan F. Meyers (*St Louis, Mo*). Hiroshi, congratulations on a terrific report and experience. I also congratulate your colleagues at Okayama University who have supported you in this. The ratio of living-donor lobar transplants to cadaveric transplants is striking, and it is out of proportion to what we are used to hearing about. Could you elaborate a little bit about the cultural situation with regard to cadaveric donors in Japan and how that might have influenced your ratio?

Dr Date. We do have a cadaveric lung transplant program, but the Japanese transplant law is the strictest in the world. It is not only a cultural problem, but many other issues are also involved. If the transplant law is going to be changed in the future and if we have a larger number of cadaveric lung transplants, the proportion between the cadaveric and LDLLTs will be changed.

Dr Vaughn A. Starnes (*Los Angeles, Calif*). Dr Date, it was an excellent paper with excellent results, and we strive to meet your results. After about 10 years in the business, I can tell you that our results are nowhere near yours. But it begs the question, with your excellent results and probably the worst recipients that you could think of, are you now going to offer this more electively to other patients?

Dr Date. Thank you very much, Dr Starnes. Certainly without your pioneering work, I would not be standing here. At this time, we are not at the stage of offering this procedure to less diseased patients because of the possible serious complications. We did have 2 rethoracotomies in donors, and we did have one patient who experienced empyema requiring a chest tube and irrigation. Therefore, we offer this only to very critically ill patients at the moment.

Dr Starnes. I have a comment about the reperfusion stage. I think that is probably the most critical stage in the operation, and the use of cardiopulmonary bypass actually helps you with that in terms of being able to come off very empty. As for our cardiac outputs and indexes, usually the first 4 to 8 hours is very low; I suspect that that is the reason you are also using nitric oxide to enhance or advance or increase the recruitment of the microvasculature of the lung bed because it really does help. I do not think it really has any "protective effect" other than vasodilatory.

Dr Federico Venuta (*Rome, Italy*). Congratulations, Dr Date, on your presentation. Which solution did you use to preserve your lungs, and did you flush them only antegradely or did you also use the retrograde flush at the time of harvesting?

Dr Date. We use Euro-Collins solution because Perfadex is not available yet, and we use an antegrade flush for about two thirds, and for the last third, we use a retrograde flush, according to your report.

Dr Duane R. Davis, Jr (*Durham, NC*). Hiroshi, congratulations again on a very impressive series.

I have a couple of questions. How much will you bend the rules in terms of your donor-recipient matching because you do not have access to cadaveric donors? The second question gets into your reperfusion injury. You had about a 20% incidence. Was that more associated with having a small lobe going into a large individual or was it more associated with your pulmonary hypertension status beforehand?

Dr Date. The first question you mentioned is how often we reject the recipient according to the donor and recipient size mismatching.

Dr Davis. Obviously if you are stuck with an adult and you do not have a good-sized donor— and I think Vaughn says 4 inches, you know, we bend the rules some—how much do you bend?

Dr Date. We accept only when the estimated FVC of the 2 grafts exceeds 45% to 50% of the predicted FVC of the recipient. Therefore, we have turned down many patients because of the size disparity. In particular, male adult patients will have very little chance to receive this operation. We have only one

adult male patient in this series. As to your second question, regarding the lung edema, we have only one patient who had a real acute lung edema immediately after reperfusion, and 5 other patients had lung edema between 5 and 10 days after transplantation, and those are the patients with primary pulmonary hypertension. Therefore I think that is not only related to the volume of the lung but also related to the cardiac function of the patient.