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Unilateral Chronic Lung Allograft Dysfunction Assessed by Biphase Computed Tomographic Volumetry in Bilateral Living-donor Lobar Lung Transplantation

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Background. Early diagnosis of unilateral chronic lung allograft dysfunction (CLAD) is difficult because the unaffected contralateral lung functions as a reservoir in bilateral living-donor lobar lung transplantation (LDLLT). We previously reported the usefulness of ¹³³Xe ventilation scintigraphy for detection of unilateral change, but the supply of ¹³³Xe has been stopped globally. The present study aimed to examine the usefulness of inspiratory and expiratory computed tomography (I/E CT) volumetry for detection of unilateral change in CLAD patients. **Methods.** This was a retrospective single-center, observational study using prospectively collected data. A total of 58 patients who underwent bilateral LDLLT from August 2008 to February 2017 were analyzed. Respiratory function tests, I/E CT were prospectively conducted. Δ Lung volume was defined as the value obtained by subtracting expiratory lung volume from inspiratory lung volume. **Results.** Fourteen (24%) cases were clinically diagnosed with CLAD, of which 10 (71%) were diagnosed as unilateral CLAD. Δ Lung volume of bilateral lungs strongly correlated with forced vital capacity ($r = 0.92$, $P < 0.01$) and forced expiratory volume in 1 second ($r = 0.80$, $P < 0.01$). Regardless the phenotypes (bronchiolitis obliterans syndrome or restrictive allograft syndrome) of CLAD, Δ lung volume onset/baseline significantly decreased compared with that in the non-CLAD group. Among the 10 unilateral CLAD patients, 3 with clinically suspected unilateral rejection yet did not show a 20% decline in forced expiratory volume in 1 second. In 2 of these, Δ lung volume of unilateral lungs on the rejection side decreased by 20% or more. **Conclusions.** Our findings suggest that I/E CT volumetry may be useful for assessment and early diagnosis of unilateral CLAD after bilateral LDLLT.

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Lung transplantation is now widely performed as a treatment for end-stage respiratory diseases. However, the survival rate of patients who undergo lung transplantation is still insufficient and lower than for those who undergo other solid organ transplantations.^{1,2}

Chronic lung allograft dysfunction (CLAD) is a major cause limiting long-term survival after lung transplantation.³⁻⁵

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Chronic lung allograft dysfunction is mainly a result of chronic rejection, and early diagnosis and treatment with immune suppressors are crucial. However, early diagnosis of any unilateral change of CLAD, especially in bilateral living-donor lung lobar transplantation (LDLLT) is difficult because the unaffected contralateral lung functions as a reservoir.

Bronchiolitis obliterans syndrome (BOS), the most common form of obstructive CLAD, is diagnosed based on a

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respiratory function test, but ventilation scintigraphy is also useful as a support tool for diagnosis. We previously reported the usefulness of ^{133}Xe ventilation scintigraphy for detection of unilateral change in BOS patients,⁶ but ^{133}Xe cannot be used in clinical practice now because the supply of nuclide (^{133}Xe) has been stopped globally. We therefore need an alternative examination method for the early diagnosis of unilateral CLAD. Various assessments of pulmonary function using imaging modalities have been reported recently, such as inspiratory and expiratory computed tomography volumetry (I/E CT volumetry),⁷⁻⁹ single photon emission CT of pulmonary perfusion and ventilation scintigraphy with technetium,¹⁰ and dual-energy Xenon CT.¹¹ Among the abovementioned, I/E CT volumetry is simple and requires no special equipment, and it has been already reported that 3D-CT imaging is useful in lung transplantation.¹² In the present study, we hypothesized that I/E CT volumetry would be able to replace ^{133}Xe ventilation scintigraphy for detection of CLAD. Hence, we examined the usefulness of I/E CT volumetry for detection of unilateral change in CLAD patients.

MATERIALS AND METHODS

This study was a retrospective single-center, observational study approved by the Ethics Committee of Kyoto University Graduate School of Medicine (R1053). A total of 63 consecutive patients who underwent bilateral LDLT from August 2008 to February 2017 in Kyoto University Hospital were enrolled. Pulmonary function tests (PFTs), I/E CT, and ^{133}Xe ventilation scintigraphy were conducted at 3, 6, and 12 months after transplantation and once yearly thereafter. The exclusion criteria included in-hospital death and death within 3 months. After application of the exclusion criteria, 58 patients were retained (Figure 1).

Chronic lung allograft dysfunction was defined as an irreversible decline in forced expiratory volume in 1 second (FEV_1) to less than 80% of baseline for 3 weeks or longer. Furthermore, although BOS was defined as just a decline in FEV_1 , restrictive allograft syndrome (RAS) was defined as a persistent decline in total lung capacity greater than 10% and/or forced vital capacity (FVC) greater than 20%.¹³

We clinically suspected CLAD when the patient had FEV_1 declines by 10% or more with or without symptom.

When we diagnosed as unilateral CLAD, the patients decreased FEV_1 by 20% or more, and they also had obviously unilateral change in imaging examination (ie, emphysematous or fibrotic change). In unilateral CLAD patients, we classified healthy side of the lung as non-CLAD lung in this study.

I/E CT Volumetry

I/E CT images were obtained during respiratory pauses at the end of maximum inspiratory effort and expiratory effort using a multidetector Aquilion 64 CT scanner (Toshiba Medical Systems, Tochigi, Japan) with 0.5-mm collimation, a scan time of 500 ms, a peak tube voltage of 120 kVp and auto-exposure control.^{9,14} I/E CT data were transferred to a workstation (SYNAPSE VINCENT; FUJIFILM, Tokyo, Japan), on which 3D lung models were reconstructed and each lung volume measured. ΔLung volume was defined as the value obtained by subtracting expiratory lung volume from inspiratory lung volume.

^{133}Xe Ventilation Scintigraphy

^{133}Xe ventilation scintigraphy was performed as previously described.¹⁵ Briefly, a gamma camera unit (Infinia; GE Healthcare, Milwaukee, WI, USA) was used to acquire posterior ventilation image from the patient after inhalation of ^{133}Xe gas (370 MBq). Two minutes after starting, washout images were acquired until 8 minutes had elapsed.

The mean transit time (MTT) was computed using height-over-area method from the washout curve, as previously described.¹⁶

Statistical Analysis

All values are presented as the mean \pm the standard deviation. Analyses were performed using JMP pro 12.2.0 software (SAS Institute, Cary, NC). To compare the means of the 3 groups, 1-way analysis of variance was performed and the Dunnett test was then conducted to determine differences. The correlations between PFTs and ΔLung volume were calculated with the Pearson product moment correlation analysis. A P value <0.05 was considered statistically significant. Sensitivity, specificity, and area under the receiver operating characteristic curve (AUC)

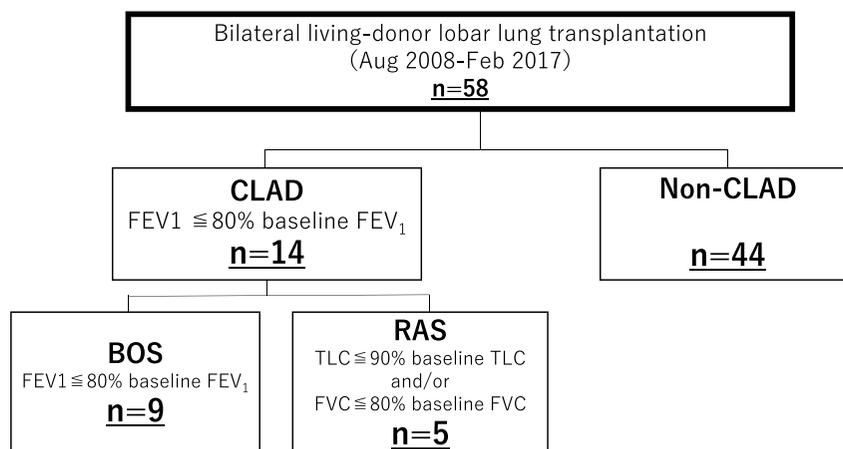


FIGURE 1. Study group cohort.

TABLE 1.**Patient characteristics**

	Non-CLAD (n = 44)	BOS (n = 9)	RAS (n = 5)	P
Mean age	39.5 ± 2.6	41.2 ± 5.7	44.4 ± 7.7	0.82
Sex male	18	6	3	0.36
Primary disease				0.89
Interstitial pneumonia	18	5	2	
Pulmonary hypertension	5	0	0	
PC after HSCT	12	1	0	
Others	9	3	3	
Size match (%)	65.0 ± 2.8	67.2 ± 6.2	62.4% ± 8.4	0.90
Unilateral/bilateral CLAD		5/4	5/0	

Size match: graft FVC/predicted %FVC.

PC, pulmonary complication; HSCT, hematopoietic stem cell transplantation.

were calculated for differentiating between the CLAD and non-CLAD groups.

RESULTS**Patient Characteristics**

Patient characteristics are shown in Table 1. No significant differences were found in mean age, gender, primary disease, and size match between non-CLAD, BOS, and RAS patients. Fourteen cases were clinically diagnosed with CLAD, of which 10 (71%) were diagnosed as unilateral CLAD.

Relationship Between CT Volumetry and PFTs

Δ lung volume of bilateral lungs was strongly related to FVC ($r = 0.92$, $P < 0.01$) and FEV₁ ($r = 0.80$, $P < 0.01$) (Figures 2A-B).

Comparison between onset or latest and baseline of Δ lung volume and inspiratory lung volume is shown in Figure 3. In both the BOS and RAS group, Δ lung volume onset/baseline was significantly decreased compared to that in the non-CLAD group. For diagnosis of CLAD, the AUC using an inward surface vector was 0.87, with an optimum cutoff of 0.80 with 73% sensitivity and 98% specificity.

¹³³Xe Ventilation Scintigraphy of Unilateral Lungs

The results of the MTT of unilateral lungs are shown in Figure 4. The MTT of BOS lungs was significantly longer than the other 2 groups (Figure 4A). Δ Lung volume of unilateral

lungs was negatively related to MTT ($r = -0.34$, $P < 0.01$) (Figure 4B).

I/E CT Volumetry in Unilateral CLAD Patients

Among the 10 unilateral CLAD patients, 1 patient was excluded by deficit data and remaining 9 patients were analyzed. Among them, 3 patients had clinically suspected rejection of the unilateral lung yet did not show a 20% decline in FEV₁. In 2 of these, Δ lung volume of unilateral lungs on the rejection side was decreased by 20% or more, and the remaining 1 case was also decreased by 15% at the time.

A representative case is shown in Figure 5. She was suspected of CLAD on the left lung at 2 years after transplant. Compared with the previous year, the left expiratory lung volume was increased, and the right was decreased, though both inspiratory lung volumes were similar. Therefore, Δ lung volume of the left lung was decreased by more than 20%, whereas Δ lung volume of the right lung was increased.

DISCUSSION

This study compared the result from I/E CT volumetry, PFTs, and ¹³³Xe ventilation scintigraphy in patients who underwent bilateral LDLT and the usefulness of I/E CT volumetry for diagnosis of unilateral CLAD. The results showed that I/E CT volumetry on both sides had a strong positive correlation with FVC and FEV₁. The MTT of ¹³³Xe ventilation scintigraphy (MTT) was useful for diagnosis of BOS and Δ lung volume of unilateral lungs had a weak correlation with MTT. Decline in Δ lung volume of bilateral lungs from baseline in CLAD patients was significantly larger than that in non-CLAD patients. Furthermore, Δ lung volume of unilateral lungs was able to detect unilateral change in CLAD patients.

A previous study has shown the usefulness of inspiratory CT volumetry in CLAD patients to differentiate RAS from BOS patients because inspiratory lung volume had a strong positive correlation with total lung capacity.¹⁷ In this study, by adding expiratory CT to inspiratory CT, it is possible to estimate FVC and FEV₁ from Δ lung volume of bilateral lungs, and it can be used for diagnosis of CLAD. It has been reported that expiratory CT can detect air trapping which is frequently observed in obstructive change.¹⁸⁻²¹ Therefore, I/E CT volumetry was able to detect not only restrictive change but also obstructive change. In BOS patients, inspiratory lung volume was gradually increased, and expiratory lung volume was also increased by emphysematous change.

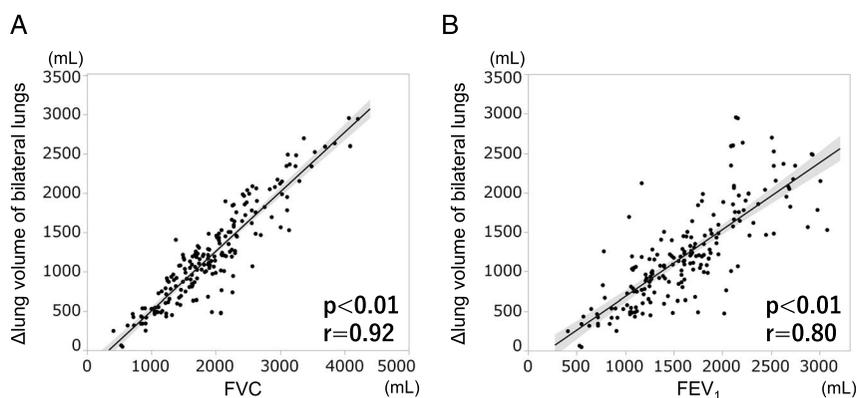


FIGURE 2. Correlation analysis (A) between Δ lung volume of bilateral lungs and FVC. (B) Between Δ lung volume of bilateral lungs and FEV₁. r, correlation coefficient.

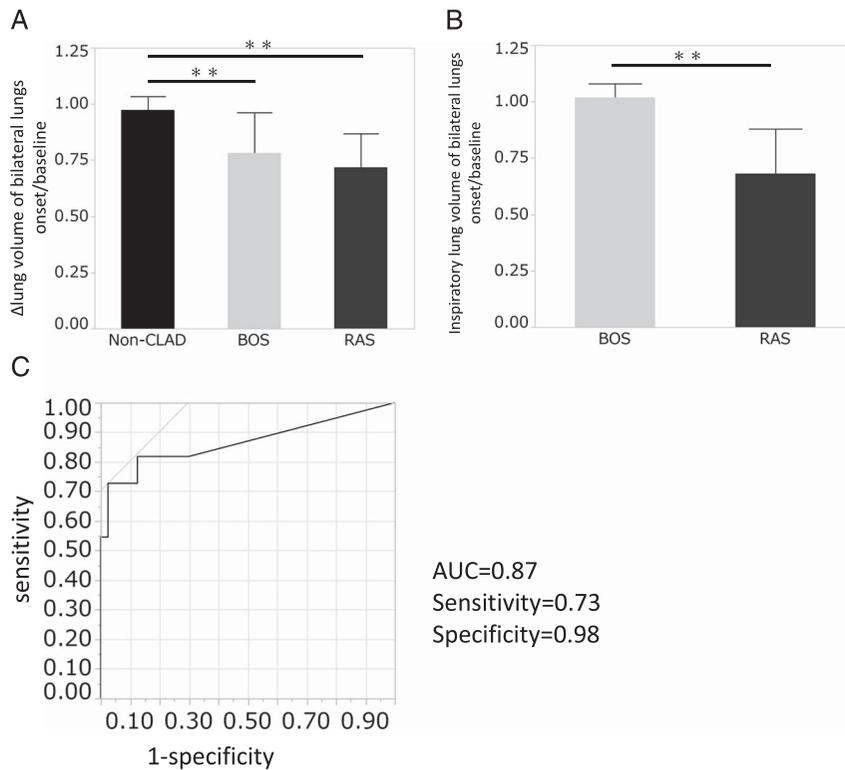


FIGURE 3. A, Δ CT volume of bilateral lungs onset or latest/baseline in the 3 groups. B, Inspiratory CT volume onset or latest/baseline. C, ROC curve analysis for diagnosis of CLAD using Δ CT volume onset or latest/baseline. Bars and error bars show mean and standard deviation; ** $P < 0.01$. ROC, receiver operating characteristic.

In RAS patients, both inspiratory lung volume and expiratory lung volume were gradually decreased because of fibrotic change, and dynamic compliance of the lungs were decreased. This is the difference between BOS and RAS.

We recommend that 20% of Δ lung volume loss should be considered CLAD because we clinically diagnosed CLAD using FEV₁ by 20% or more from the baseline. Furthermore, in ROC curve analysis for differentiating between CLAD and non-CLAD group using Δ lung volume onset or latest/baseline, the cutoff value that maximizes AUC was 0.80 with high specificity (98%), but not so high sensitivity (73%). In this study and setting, 2 of 9 unilateral CLAD cases could be early diagnosed by I/E CT volumetry.

There were some cases in which FEV₁ was decreased, but Δ lung volume was not decreased. Among them, the MTT

was not extended in this study. It seemed that detection of obstructive changes without air trapping was difficult with I/E CT volumetry. However, air trapping is a characteristic finding in BOS patients, and the ability to detect air trapping is one of the reasons for high specificity of diagnosis. It is likely that ventilation scintigraphy, with its ability to be evaluated by integrating multiple breaths, might have higher sensitivity to detect obstructive change than I/E CT volumetry, but we can no longer use it.

The I/E CT volumetry data were also affected by other lung diseases. For example, there was a case who had pneumonia and decreased Δ lung volume in this study. After the treatment of pneumonia, Δ lung volume was improved but not as much as before and lung injury (scarring) on pneumonia was remained in this case.

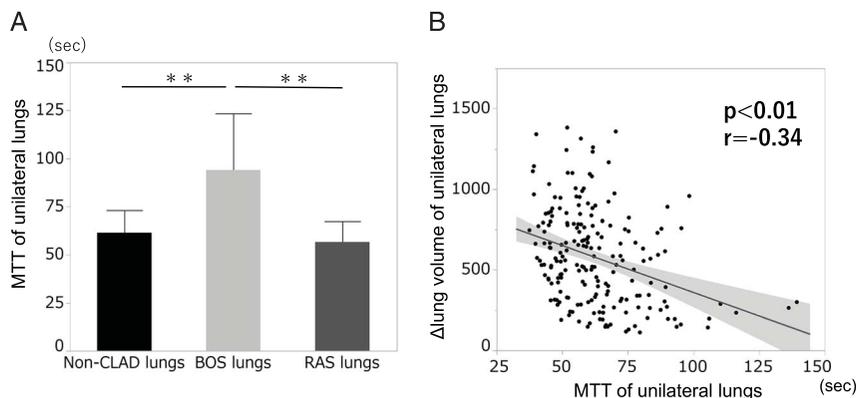


FIGURE 4. A, MTT of unilateral lungs divided into the 3 groups, non-CLAD lungs, BOS lungs, and RAS lungs. B, Correlation analysis between Δ lung volume of unilateral lungs and MTT of unilateral lungs. Bars and error bars show mean and standard deviation; * $P < 0.05$, ** $P < 0.01$. r: correlation coefficient.

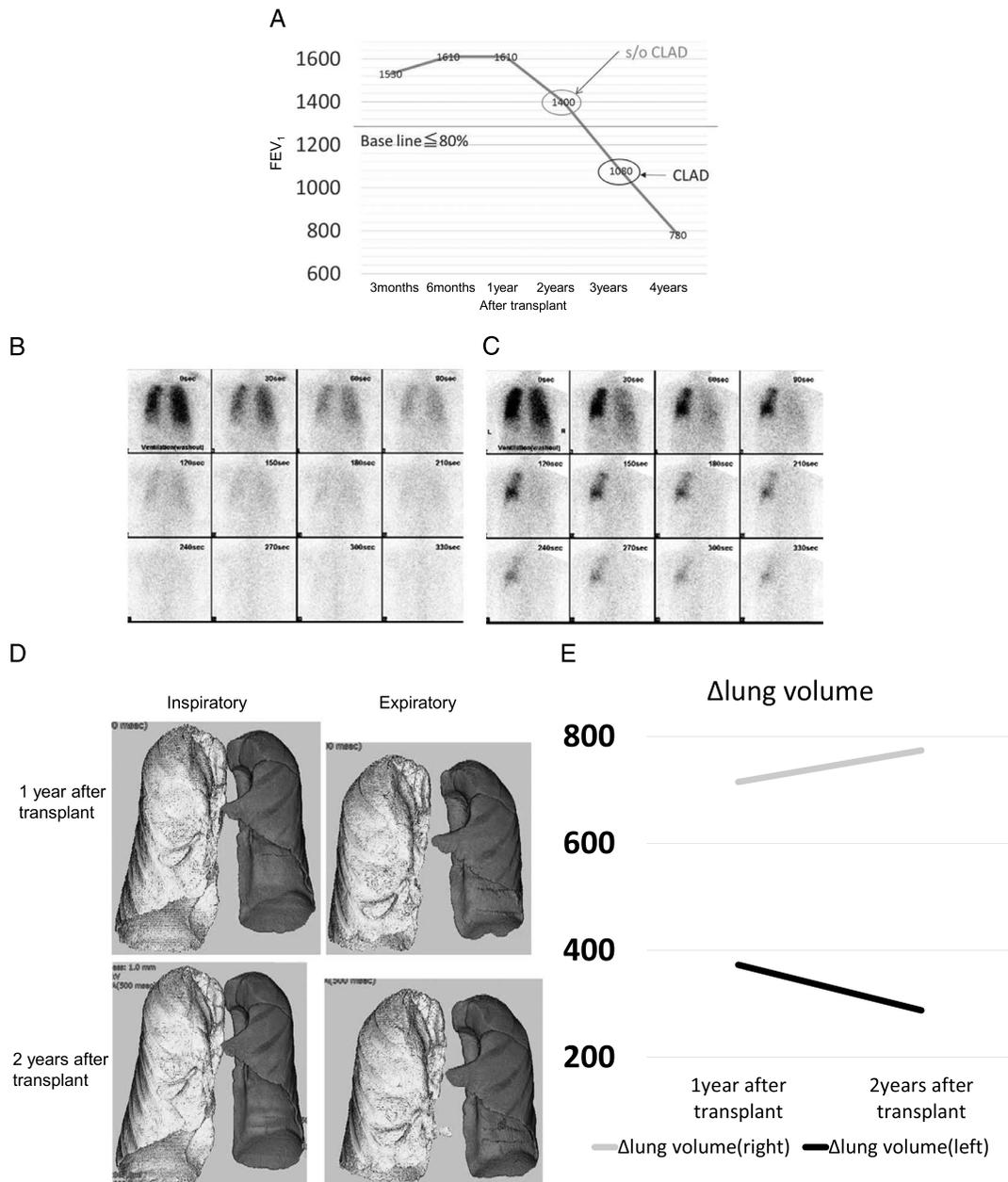


FIGURE 5. Representative case of unilateral CLAD. A, Posttransplant course of FEV₁. B, ¹³³Xe ventilation scintigraphy 1 year after transplant. C, ¹³³Xe ventilation scintigraphy 2 years after transplant. D, I/E CT volumetry at 1 year and 2 years after transplantation. E, Δ lung volume 1 year and 2 years after transplant.

Δ Lung volume can be measured not only in both lungs but also in localized areas, such as 1 lung or 1 lobe, and it is possible to estimate the regional lung function and to detect unilateral CLAD. This is the advantage of using I/E CT volumetry. We think these results are applicable on single lung transplantation, and we plan to collect the data in cadaveric single lung transplantation patients.

Previously, it was difficult to evaluate the respiratory function of lung regions, but I/E CT volumetry allows us to analyze the regional lung function. Evaluation of lung function using imaging modality is expected to progress further in the future.¹¹ Specifically, evaluation of the total respiratory phase with 4DCT and evaluation of airflow in xenon contrast CT may be useful as well.²²

Several limitations of this study should be acknowledged. First, it is difficult to stop breathing in patients whose

respiratory function is significantly low, and it is uncertain whether the inspiratory phase or the expiratory phase at the time of each scan. However, since I/E CT is aimed at early detection of CLAD, it is probable that patients with worse lung function have already been diagnosed and treated, and it will not fit for this study purpose.

Second, inspiratory CT and expiratory CT imaging double the usual exposure dose. However, ultralow dose CT has become available for CT volumetry, and the exposure dose is expected to be further reduced with the development of technology in the future.^{23,24}

Third, some patients with pulmonary complication other than CLAD (eg, pneumonia) decreased Δ lung volume. However, we were able to use CT imaging by I/E CT and diagnose it appropriately.

In conclusion, our findings suggest that I/E CT volumetry is able to predict the unilateral pulmonary function in patients with LDLT. I/E CT volumetry is useful for assessment of CLAD in which change occurs only unilaterally. In this study, we examined patients who underwent bilateral LDLT. It may be useful also in single lung transplantation from cadaveric donors.

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