



Comparison between quantitative computed tomography, scintigraphy, and anatomical methods for prediction of postoperative FEV₁ and DLCO: effects of chronic obstructive pulmonary disease status and resected lobes

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Background: Postoperative assessment of pulmonary function is important for estimating the risk of thoracic surgery and long-term disability following pulmonary resection, including predicted postoperative (ppo) forced expiratory volume (FEV) in one second (ppoFEV₁) and percent predicted lung diffusion capacity for carbon monoxide (ppo%DLCO) estimation. The ppo values were compared using four different estimation methods between chronic obstructive pulmonary disease (COPD) and non-COPD patients and according to the resected lobe.

Methods: This prospective study included 59 eligible patients requiring single lobectomy and succeeded in performing pulmonary function tests at 3 and 12 months after lobectomy. The ppoFEV₁ and ppo%DLCO were compared with poFEV₁ and po%DLCO obtained at 3 and 12 months after lobectomy. The ppo values were estimated using the four usual methods: the 19-segment anatomical technique (S), perfusion scintigraphy (Q), quantitative CT (CT), and quantitative CT with low attenuation volume (CT_{LAV}) subtraction.

Results: For non-COPD and COPD patients, the smallest mean difference between ppo and po values was observed by S for FEV₁ and %DLCO. Based on the resected lobe, the smallest mean difference was observed by (I) Q for right upper lobectomy (RUL) excluding %DLCO at 12 months by S, (II) S for left upper lobectomy (LUL), (III) CT and CT_{LAV} for right lower lobectomy (RLL), and (IV) CT and CT_{LAV} for left lower lobectomy (LLL) at 12 months. The ppo values calculated by S for RUL (FEV₁ at 3 and 12 months and %DLCO at 3 months) and by all four methods for LLL (FEV₁ and %DLCO at 3 months) were smaller than the po values.

Conclusions: The S method is adequate for calculating ppoFEV₁ and ppo%DLCO when patients are classified as non-COPD and COPD. However, S sometimes overestimates the ppoFEV₁ and ppo%DLCO when patients are classified according to the resected lobe. The CT_{LAV} method may be the method of choice instead of S for calculating ppoFEV₁ and ppo%DLCO in patients who undergo lung lobectomy despite the presence or absence of airflow limitation.

Keywords: Thoracic surgical candidate; video-assisted thoracoscopic surgery (VATS); location of the lobe

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Introduction

Surgical lung resection is the recommended treatment for non-metastatic, non-small cell lung cancer patients. Postoperative (po) evaluation of pulmonary function is important for estimating the risk of thoracic surgery and long-term disability after pulmonary resection. The guidelines of the European Respiratory Society and the European Society of Thoracic Surgery (ERS/ESTS) recommend the use of the following po values: forced expiratory volume in 1 second (FEV₁), lung diffusion capacity for carbon monoxide (DLCO), and maximal oxygen consumption ($\dot{V}O_2$ max) to estimate the risk of death and cardiopulmonary complications after surgical resection (1). In clinical practice, the most common and widely used functional test is estimation of the predicted postoperative (ppo) FEV₁ and DLCO.

In a patient undergoing lobectomy, the “anatomical method” based on the number of segmental bronchi (2) is used to calculate the ppoFEV₁ and ppoDLCO. Currently, other methods, based on scintigraphy or computed tomography (CT) imaging, are considered to estimate po respiratory function more accurately (3-8). However, these investigations do not focus on whether patients were diagnosed with chronic obstructive pulmonary disease (COPD) or were non-COPD, or the location of the resected lobe, although lung expansion and alternation of pulmonary function after lobectomy were reported to differ according to the volume of emphysematous lung parenchyma (9,10) and the area of the resected lobe (11,12).

The primary objective of this prospective study was to evaluate ppoFEV₁ and ppo%DLCO with four different estimation methods between non-COPD and COPD patients and according to the resected lobe. These estimates were compared to FEV₁ and %DLCO measured at 3 and 12 months postoperatively (poFEV₁ and po%DLCO) after single lobectomy.

We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/jtd-20-1280>).

Methods

Patients

Eligible patients were those scheduled to undergo single lobectomy by video-assisted thoracoscopic surgery (VATS) at Kitasato University Hospital in Kanagawa, Japan, between December 11, 2013 and March 28, 2016, and those who succeeded in performing pulmonary function tests at 3 and 12 months after lobectomy. This study was approved by the Kitasato University Medical Ethics Organization on June 28, 2013 (approval number: KMEO B13-110). All patients were prospectively enrolled in this study after obtaining their written informed consent. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Using the “Algorithm for Thoracotomy and Major Anatomical Resection” (2), high-risk patients (ppoFEV₁ or ppo%DLCO <30%) were excluded as candidates for surgical treatment in our hospital. Patients were given an incentive spirometer before surgery according to the standard protocol for thoracic surgery in our hospital. However, they did not undergo focused perioperative or pulmonary rehabilitation before or after the surgery. For smoking status, a patient who had smoked more than 100 cigarettes in their lifetime and had smoked in the last 28 days before preoperative pulmonary function testing, was defined as a “current smoker.” A patient who had smoked more than 100 cigarettes in their lifetime but had not smoked in the last 28 days before preoperative pulmonary function testing was defined as a “former smoker,” and a patient who had smoked less than 100 cigarettes in their lifetime and did not currently smoke was defined as a “non-smoker.”

Pulmonary function tests

Pulmonary function tests including slow vital capacity (SVC), forced vital capacity (FVC), FEV₁, and DLCO were performed according to the guidelines of the Japanese Respiratory Society (13), and spirometric reference values of SVC, FVC, FEV₁, and FEV₁/FVC for Japanese adults

were calculated using the LMS (lambda, mu, sigma) method (14). DLCO was corrected according to the patient's haemoglobin level. To determine %DLCO, normal values of DLCO reported by Burrows *et al.* (15) were applied.

FEV₁ and %DLCO were evaluated before the operation and at 3 and 12 months postoperatively with the same equipment and technique. We decided to perform the pulmonary function tests at 3 months postoperatively for the short-term follow-up. In some patients, the symptoms and pulmonary function kept improving until 12 months postoperatively. Thus, we decided to perform the pulmonary function tests at 12 months for the long-term follow-up and compared them to the ppo values.

A preoperative pulmonary function test was performed within one month prior to the surgery. Classification of airflow limitation severity in COPD was defined with post-bronchodilator predicted FEV₁ according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (16). Among patients with airflow limitation (FEV₁/FVC <0.70), some patients who were previously diagnosed with COPD and had been started on treatment for their COPD, refused to undergo the bronchodilator test to assess their airflow limitation severity. Other patients that were not diagnosed with an obstructive ventilatory defect were started on treatment with a bronchodilator [inhaled long-acting muscarinic antagonist (LAMA) and/or long-acting beta-agonist (LABA)] without a bronchodilator test. The preoperative pulmonary function test was repeated approximately 2 weeks after receiving treatment with a bronchodilator, which was maintained throughout the study. The patients who remained with airflow limitation (FEV₁/FVC <0.70) under the bronchodilator treatment were regarded as having COPD, and their airflow limitation severity was assessed on the basis of results of the second preoperative pulmonary function test. The percentage predicted FEV₁ and DLCO were expressed as the percentage of the predicted values for age, sex, and height.

Computed tomography (CT) scanning

With the patient in the supine position, helical CT scans with 1.25-mm high-resolution CT images of lung during a deep inspiratory breath hold using 64-detector row CT scanners (Optima 660; GE Healthcare, Tokyo, Japan) with 512×512 matrices, 1.25-mm collimation, and a scan time of 0.5 s at 120 kVp and 270 mA were obtained. Since this was a routine practice, patients were not exposed to

any additional radiation for the purpose of measuring the radiological parameters in this study.

Image interpretation and data analysis

Three-dimensional volume rendering lung images were created using a commercially available, user-friendly imaging software program (Ziostation 2[®]; Ziosoft, Inc., Tokyo, Japan). Threshold limits of -600 to -1,024 HU were applied to segment both lungs entirely and to exclude the soft tissues surrounding the lungs and the large vessels, atelectasis, fibrosis, and tumours within the lung. The volume of a lung segmented by a certain threshold limit can be readily obtained with the imaging software program. The volume of the lungs (-600 to -1,024 HU) was designated as the total lung volume (TLV). The lungs were divided into two areas: low-attenuation areas that represented emphysematous lung tissue (<-950 HU), and normal-attenuation areas (-600 to -950 HU) that represented normal lung fields. The volume and the low-attenuation volume (LAV) for each lobe and lung were calculated. %LAV of the resected lobe was calculated by dividing [LAV of the resected lobe] by [volume of the resected lobe] and %LAV of lung was calculated by dividing [LAV of the lung] by [volume of the lung] (12).

Prediction of the postoperative pulmonary function

For FEV₁ and %DLCO, the ppo values were all calculated from pre-operative values modified by estimation of lost function using 4 techniques: an algorithmic method based on preoperative spirometry, a method based on the lung perfusion scintigraphy assessed by technetium-99m macro-aggregated albumin (99mTc-MAA), and 2 methods based on quantitative CT.

The Algorithmic method based on preoperative spirometry was (I) calculated based on the number of functioning/unobstructed segments to be removed during surgery (S): ppo value = preoperative value × (1-y/z), with [y] the number of functional or unobstructed lung segments to be removed and [z] the total number of functional segments (1,2).

(II) The method based on perfusion scintigraphy (Q) was as follows: ppo value = preoperative value × (1 - functional contribution of perfusion of the region to be removed). This is the standard calculation formula for thoracic surgery in our hospital (17).

(III) The methods based on quantitative CT estimated

the ppo value according to the following formula (CT): ppo value = preoperative value $\times \{1 - (\alpha/\gamma)\}$, with $[\alpha]$ the regional functional lung volume of the lobe to be removed, and $[\gamma]$ the lung volume (7); and (IV) quantitative CT with LAV (CT_{LAV}): ppo value = preoperative value $\times (1 - \{[\alpha \times (1 - \beta)]/\gamma\})$, with $[\alpha]$ the regional functional lung volume of the lobe to be removed, $[\beta]$ the fraction of the LAV of the lobe to be removed, and $[\gamma]$ the lung volume (18).

These four ppo values were compared to the actual po values obtained at 3 and 12 months after lobectomy.

Statistical analysis

To evaluate the characteristics of the patients, preoperative data were compared between the non-COPD and COPD groups using the Mann-Whitney U test (one-tail).

Agreement between the ppo values and po values of FEV₁ and %DLCO obtained at 3 and 12 months after lobectomy were analysed using the Bland-Altman method (19) by plotting the difference between the paired po and ppo values according to COPD, non-COPD and the resected lobe. Limits of agreement (LOA) were defined as mean of difference ± 2 SD. The mean values for FEV₁ and %DLCO were also compared between the ppo and po values using the determination coefficient. The mean differences between the ppo and po values are expressed as mean standard deviation for each method. A P value <0.05 was considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 3.0.2) (20) based on a modified version of R commander (version 2.4-0).

Results

Preoperative data

Of the 75 patients eligible for VATS lobectomy, 16 were excluded because of chylothorax (n=1), pyothorax (n=2), lung cancer recurrence (n=3), cerebral vascular infarction (n=1), renal cell carcinoma (n=2), and withdrawal of consent (n=7). Finally, 59 patients (mean age, 69.0 \pm 8.2 years; range, 43–84 years) with complete pulmonary function assessment were included in this study. The indications for lobectomy were adenocarcinoma (n=44), squamous cell carcinoma (n=10), adenosquamous carcinoma (n=1),

small-cell carcinoma (n=1), large cell neuroendocrine carcinoma (n=1), pleomorphic carcinoma (n=1), and benign lymphoproliferative disorder (n=1). Preoperative patient characteristics are described in *Table 1*. Current and former smokers discontinued their smoking habits before surgery. Most of the patients, including 16 of 20 non-COPD patients and 17 out of 20 COPD patients, discontinued smoking more than 4 weeks prior to the preoperative pulmonary function tests. The remaining 7 out of 40 patients discontinued smoking just after the first set of pulmonary function tests. According to the guidelines for lung function testing (13), all patients discontinued smoking 24 hours prior to DLCO measurements of the first set of pulmonary function tests to prevent smoking from affecting the results of the test (21,22). Thereafter, none of them resumed smoking.

Body weight was higher in the COPD group than in the non-COPD group. However, FEV₁, FEV₁/FVC, %FEV₁, %DLCO, and %DLCO/V_A were lower in the COPD group than in the non-COPD group (*Table 1*).

Both mean %LAV values of the resected lobe and lung were higher in the COPD than in the non-COPD group. There was no difference between the groups for the LAV ratio between the resected lobe and the lung (LAV of the resected lung/LAV of the lung).

VATS for lobectomy and postoperative pain

Pure VATS using a 3-port technique was performed in 13 patients (9 non-COPD, 4 COPD patients) by four thoracic surgeons, and Assist VATS was performed in 46 patients by seven thoracic surgeons. Pure VATS was performed for 6 right upper lobectomies (RUL), 6 right lower lobectomies (RLL), and 1 left lower lobectomy (LLL). No patient underwent conversion from VATS to open thoracotomy. Epidural analgesia was used during the surgeries. All patients received patient-controlled epidural analgesia (PCEA) until postoperative day (POD) 2 or 3. Thereafter, non-steroidal anti-inflammatory drugs and/or opioid pain medications, such as tramadol hydrochloride, were administered during the hospitalization period, on an “as required” basis until 8 weeks after surgery. The pulmonary function tests performed at 3 months and 12 months after surgery were performed under pain-free conditions and no patient complained of postoperative pain during the pulmonary function tests.

Table 1 Preoperative characteristics of patients

Variable	Non-COPD	COPD	P value
Number of patients	31	28	
Age (years)	69.5±9.8	69.8±7.3	0.311
Height (cm)	159.0±9.0	161.7±8.7	0.107
Body weight (kg)	56.8±9.9	61.4±9.8	0.037
Smoking index (pack-years)	25.3±30.5	39.4±36.6	0.055
Non-smokers	11	8	
Current or former smokers	20	20	
SVC (L)	3.29±0.772	3.45±0.67	0.256
%SVC (%)	98.5±15.4	102.2±11.1	0.256
FVC (L)	3.10±0.82	3.37±0.65	0.062
%FVC (%)	99.9±17.3	103.8±11.0	0.062
FEV ₁ (L)	2.47±0.52	2.11±0.39	0.035
FEV ₁ /FVC (%)	76.2±4.9	61.3±6.9	<0.001
%FEV ₁ (%)	100.0±15.8	86.1±19.9	<0.001
%DLCO (%)	116.3±30.7	108.3±26.1	0.035
%DLCO/V _A (%)	99.4±24.5	88.6±21.5	0.010
%LAV of the resected lobe (%)	2.7±6.1	3.4±3.6	0.005
%LAV of the lung (%)	1.7±2.9	3.3±3.5	0.004
LAV of the resected lobe/LAV of the lung (%)	18.0±14.1	20.7±14.2	0.219

Values are represented mean ± SD. A P value of less than 0.05 was considered statistically significant. COPD, chronic obstructive pulmonary disease; %DLCO, percent predicted lung diffusion capacity for carbon monoxide; %DLCO/V_A, percent predicted lung diffusion capacity for carbon monoxide divided by the alveolar volume; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; LAV, low-attenuation volume; SVC, slow vital capacity.

Pulmonary function and symptoms after lobectomy

One GOLD 1 COPD patient who underwent LLL developed pneumonia on POD 6. He was treated with antibiotics for 7 days and had an uneventful recovery. He required low-flow oxygen therapy but did not require mechanical ventilation. Other patients did not suffer from postoperative complications such as pneumonia and did not require mechanical ventilation postoperatively. One GOLD 1 and two GOLD 2 COPD patients who had LUL required domiciliary oxygen therapy at the time of hospital discharge, which was withdrawn within 3 months after surgery and the three of them had quit smoking several years ago. No patients required oxygen therapy following pulmonary function tests post-lobectomy.

Predicted postoperative and actual postoperative values at 3 and 12 months after lobectomy

The ppo FEV₁ and %DLCO and mean volume differences with po values were calculated for each method of assessment.

Non-COPD and COPD patients

The ppoFEV₁ calculated by S, Q, CT, and CT_{LAV}, the mean differences between po and ppo (bias) and LOA and determination coefficient are shown in *Table 2*. In the non-COPD group, S showed the smallest mean difference of FEV₁ at 3 and 12 months after lobectomy. In the COPD group, S again showed the smallest mean difference of FEV₁ at 3 and 12 months after lobectomy.

The ppo%DLCO calculated by S, Q, CT, and CT_{LAV},

Table 2 ppoFEV₁, mean differences between the ppo and po values at 3 and 12 months after lobectomy and the limit of agreement

Method of estimation	ppoFEV ₁ (L)	Mean difference with poFEV ₁ (L), 3M	Limit of agreement -2SD, 2SD (L)	Determination coefficient	Mean difference with poFEV ₁ (L), 12M	Limit of agreement -2SD, 2SD (L)	Determination coefficient
Non-COPD							
S	1.89±0.49	0.02±0.23	-0.43, 0.49	R ² =0.73; P<0.01	0.11±0.27	-0.49, 0.67	R ² =0.69; P<0.01
Q	1.87±0.49	0.05±0.21	-0.37, 0.47	R ² =0.75; P<0.01	0.13±0.26	-0.46, 0.69	R ² =0.71; P<0.01
CT	1.87±0.49	0.05±0.22	-0.38, 0.48	R ² =0.68; P<0.01	0.14±0.27	-0.48, 0.7	R ² =0.73; P<0.01
CT _{LAV}	1.88±0.51	0.03±0.22	-0.40, 0.47	R ² =0.79; P<0.01	0.12±0.28	-0.50, 0.69	R ² =0.74; P<0.01
COPD							
S	1.68±0.30	0.08±0.31	-0.55, 0.7	R ² =0.44; P<0.01	0.12±0.34	-0.56, 0.79	R ² =0.36; P<0.01
Q	1.67±0.32	0.09±0.31	-0.52, 0.7	R ² =0.45; P<0.01	0.13±0.34	-0.55, 0.8	R ² =0.35; P<0.01
CT	1.65±0.36	0.11±0.32	-0.53, 0.76	R ² =0.45; P<0.01	0.15±0.35	-0.54, 0.85	R ² =0.36; P<0.01
CT _{LAV}	1.67±0.36	0.09±0.31	-0.54, 0.73	R ² =0.44; P<0.01	0.13±0.34	-0.55, 0.82	R ² =0.35; P<0.01

Values are represented as mean ± SD. COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in one second; LAV, low-attenuation volume; Limit of agreement, mean ± 2SD; M, months; po, postoperative value; ppo, predicted postoperative value.

Table 3 ppo%DLCO, mean differences between the ppo and po values at 3 and 12 months after lobectomy and the limit of agreement

Method of estimation	ppo%DLCO (%)	Mean difference with po%DLCO (%), 3M	Limit of agreement -2SD, 2SD (%)	Determination coefficient	Mean difference with po%DLCO (%), 12M	Limit of agreement -2SD, 2SD (%)	Determination coefficient
Non-COPD							
S	97.0±23.7	0.9±15.2	-28.80, 31.39	R ² =0.62; P<0.01	10.7±15.8	-20.50, 43.10	R ² =0.60; P<0.01
Q	95.7±22.4	2.2±14.5	-26.18, 31.27	R ² =0.62; P<0.01	12.0±15.4	-18.39, 43.49	R ² =0.64; P<0.01
CT	95.8±23.3	2.0±14.2	-26.57, 31.21	R ² =0.65; P<0.01	11.8±14.8	-18.60, 43.25	R ² =0.66; P<0.01
CT _{LAV}	96.4±23.5	1.4±14.4	-27.67, 31.06	R ² =0.64; P<0.01	11.2±14.8	-19.10, 42.5	R ² =0.67; P<0.01
COPD							
S	86.4±21.5	1.8±12.8	-23.77, 27.37	R ² =0.70; P<0.01	7.6±11.7	-15.87, 31	R ² =0.76; P<0.01
Q	85.7±21.6	2.4±13.1	-23.69, 28.58	R ² =0.72; P<0.01	8.2±12.2	-16.08, 32.5	R ² =0.76; P<0.01
CT	84.1±20.6	4.1±14	-23.21, 31.73	R ² =0.64; P<0.01	9.8±14.5	-18.58, 38.62	R ² =0.60; P<0.01
CT _{LAV}	84.9±20.5	3.2±13.5	-23.10, 29.9	R ² =0.67; P<0.01	9.0±14.1	-18.69, 37.03	R ² =0.60; P<0.01

Values are represented as mean ± SD. COPD, chronic obstructive pulmonary disease; %DLCO, percent predicted lung diffusion capacity for carbon monoxide; LAV, low-attenuation volume; Limit of agreement, mean ± 2SD; M, months; po, postoperative value; ppo, predicted postoperative value.

mean differences between po and ppo, and LOA and determination coefficient are shown in *Table 3*. In the non-COPD group, S showed the smallest mean difference of %DLCO at 3 and 12 months after lobectomy. In the COPD group S again showed smallest mean difference of %DLCO at both 3 and 12 months after lobectomy.

According to resected lobe

The RUL, right middle lobectomy (RML), RLL, LUL and LLL were performed for 19, 2, 15, 14, and 9 patients, respectively (*Table 4*). Among these patients, the mean volume of resected lobe, volume percentage ratio of LAV of resected lobe to LAV of the lung (%), and the volume of

Table 4 Volume of lobe and segment, and percentage of low-attenuation volume of the resected lobe compared to the lung

	Right upper lobe	Right middle lobe	Right lower lobe	Left upper lobe	Left lower lobe
Number of patients (non-COPD/ COPD)	19 (14/5)	2 (1/1)	15 (10/5)	14 (3/11)	9 (3/6)
Volume of lobe (L), mean \pm SD (range)	0.94 \pm 0.29 (0.53–0.16)	0.52 \pm 0.05 (0.48–0.55)	0.88 \pm 0.21 (0.62–1.4)	1.23 \pm 0.34 (0.69–1.74)	0.91 \pm 0.26 (0.56–1.44)
LAV of the resected lobe/LAV of the lung (%), mean \pm SD (range)	21.1 \pm 17.4 (6.0–73.5)	32.5 \pm 8.2 (26.8–38.3)	11.9 \pm 8 (3.3–27.4)	28.0 \pm 11.1 (15.3–55.7)	12.4 \pm 9.2 (2.6–28.5)
Volume of segment (L), mean \pm SD (range)	0.31 \pm 0.1 (0.18–0.54)	0.26 \pm 0.24 (0.24–0.28)	0.21 \pm 0.059 (0.12–0.28)	0.23 \pm 0.06 (0.14–0.35)	0.23 \pm 0.08 (0.14–0.36)

Values are represented as mean \pm SD. The volume of segment was calculated by dividing [volume of lobe] by [number of segmental bronchi]. LAV, low attenuation volume; COPD, chronic obstructive pulmonary disease.

each pulmonary segment, which was calculated by dividing [volume of each lobe] by [number of segmental bronchi], are also shown in *Table 4*. The mean ratio of LAV of each resected lobe/lung varied between 2.6% and 73.5%. The upper lobes, especially the left upper lobe (28.0%), had higher %LAV values than the lower lobes (11.9 and 12.4%).

The ppoFEV₁ and ppo%DLCO calculated by S, Q, CT and CT_{LAV}; mean difference between po and ppo and LOA and determination coefficient are shown in *Tables 5* and *6*. The patients with RML were excluded from statistical analysis because of the small number of subjects.

For RUL, Q showed the smallest mean positive difference of FEV₁ at 3 and 12 months after lobectomy. Q also showed the smallest mean positive difference of %DLCO at 3 months, and S showed the smallest mean difference %DLCO at 12 months after lobectomy. At both 3 and 12 months after lobectomy, poFEV₁ was less than ppoFEV₁ calculated by S. At 3 months after lobectomy, po%DLCO was also less than ppo%DLCO calculated by S.

For RLL, CT and CT_{LAV} showed the smallest mean difference of FEV₁ at 3 and at 12 months after lobectomy. CT_{LAV} also showed the smallest mean difference of %DLCO at 3 and 12 months after lobectomy.

For LUL, S showed the smallest mean difference of FEV₁ at 3 and 12 months after lobectomy. S also showed the smallest mean difference of %DLCO at 3 and 12 months after lobectomy.

For LLL, the actual FEV₁ at 3 months after lobectomy was less than the ppoFEV₁ calculated by all 4 methods. In contrast, CT and CT_{LAV} showed the smallest mean difference of FEV₁ at 12 months after lobectomy. Similarly, the po%DLCO was less than the ppo%DLCO calculated by all four different techniques at 3 months after lobectomy.

The CT_{LAV} showed the smallest mean difference of %DLCO at 12 months after lobectomy.

Quantitative CT with and without low attenuation volume assessment

For both FEV₁ and %DLCO, CT_{LAV} showed a larger ppo value than CT, and CT_{LAV} showed a smaller mean difference value than CT in both non-COPD and COPD groups, and in any area of lobe resection (*Tables 2,3,5,6*).

Discussion

Pulmonary function has been reported to improve from 3 to 12 months after lobectomy; however, FEV₁ and %DLCO at 12 months after lobectomy were still lower than pre-operative values (12). After lung resection, alterations of pulmonary function are in turn implicated in the development of postoperative complications, which are among the foremost causes of mortality (23). In addition, COPD patients sometimes suffer acute exacerbations which worsen pulmonary function (24). Therefore, excluding the estimation method that provided overestimated ppo values compared to the po values is presumed to be better, because lung surgery candidates selected by overestimated ppo values will have narrow safety margins owing to postoperative complications and acute exacerbations.

Several studies have evaluated the feasibility and accuracy of quantitative CT estimation of ppoFEV₁ and DLCO, confirming the validity of this assessment technique (3-8). However, these previous studies did not focus on whether patients were diagnosed with COPD, or the location of the resected lobe, although the po lung volume and its function may vary depending on LAV (9,10) and the area of the

Table 5 ppoFEV₁, mean differences between the ppo and po values at 3 and 12 months after lobectomy and the limit of agreement

Method of estimation	ppoFEV ₁ (L)	Mean difference with poFEV ₁ (L), 3M	Limit of agreement -2SD, 2SD (%)	Determination coefficient	Mean difference with poFEV ₁ (L), 12M	Limit of agreement -2SD, 2SD (%)	Determination coefficient
RUL							
S	1.94±0.43	-0.01±0.22	-0.45, 0.43	R ² =0.77; P<0.01	-0.00±0.25	-0.50, 0.49	R ² =0.55; P<0.01
Q	1.90±0.19	0.02±0.19	-0.36, 0.41	R ² =0.79; P<0.01	0.03±0.25	-0.47, 0.53	R ² =0.56; P<0.01
CT	1.83±0.45	0.10±0.2	-0.30, 0.5	R ² =0.80; P<0.01	0.11±0.27	-0.43, 0.65	R ² =0.54; P<0.01
CT _{LAV}	1.85±0.48	0.08±0.2	-0.33, 0.48	R ² =0.80; P<0.01	0.08±0.27	-0.46, 0.62	R ² =0.58; P<0.01
RLL							
S	1.60±0.38	0.15±0.26	-0.37, 0.67	R ² =0.62; P<0.01	0.24±0.27	-0.30, 0.78	R ² =0.69; P<0.01
Q	1.61±0.4	0.14±0.25	-0.36, 0.63	R ² =0.65; P<0.01	0.23±0.27	-0.31, 0.77	R ² =0.72; P<0.01
CT	1.72±0.48	0.03±0.26	-0.48, 0.55	R ² =0.78; P<0.01	0.12±0.29	-0.46, 0.71	R ² =0.79; P<0.01
CT _{LAV}	1.72±0.48	0.03±0.25	-0.48, 0.53	R ² =0.78; P<0.01	0.12±0.29	-0.46, 0.7	R ² =0.79; P<0.01
LUL							
S	1.69±0.31	0.09±0.21	-0.33, 0.52	R ² =0.60; P<0.01	0.17±0.27	-0.38, 0.72	R ² =0.42; P<0.01
Q	1.67±0.32	0.12±0.22	-0.33, 0.57	R ² =0.53; P<0.01	0.19±0.29	-0.39, 0.77	R ² =0.35; P<0.01
CT	1.58±0.29	0.19±0.23	-0.27, 0.67	R ² =0.52; P<0.01	0.26±0.28	-0.30, 0.84	R ² =0.29; P<0.01
CT _{LAV}	1.61±0.29	0.16±0.23	-0.29, 0.64	R ² =0.52; P<0.01	0.24±0.28	-0.33, 0.82	R ² =0.29; P<0.01
LLL							
S	1.79±0.37	-0.04±0.44	-0.92, 0.84	R ² =0.27; P<0.01	0.02±0.48	-0.84, 0.97	R ² =0.32; P=0.06
Q	1.77±0.37	-0.03±0.43	-0.88, 0.83	R ² =0.27; P<0.01	0.04±0.48	-0.92, 0.99	R ² =0.32; P=0.06
CT	1.81±0.38	-0.05±0.44	-0.93, 0.79	R ² =0.23; P<0.01	0.01±0.48	-0.97, 0.95	R ² =0.30; P=0.07
CT _{LAV}	1.82±0.38	-0.05±0.44	-0.93, 0.78	R ² =0.23; P<0.01	0.01±0.48	-0.97, 0.95	R ² =0.30; P=0.07

Values are represented as mean ± SD. RUL, right upper lobectomy; RLL, right lower lobectomy; LUL, left upper lobectomy; LLL, left lower lobectomy. COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in one second; LAV, low-attenuation volume; Limit of agreement, mean ± 2 SD; M, months; po, postoperative value; ppo, predicted postoperative value.

resected lobe (11,12).

Comparison between non-COPD and COPD

Ueda *et al.* (4) compared ppoFEV₁ estimated by quantitative CT and Nakahara formula (25) with the po value measured 3–4 months after surgery for 30 patients undergoing surgical resection of lung cancer, including lobectomy and segmentectomy. Wu *et al.* (7) compared the quantitative CT ppoFEV₁, excluding emphysematous lesions, with perfusion scintigraphy based on preoperative spirometry and the po values were measured 3 months after the surgery for 44 non-COPD patients undergoing surgical resection of lung

cancer, including 16 lobectomies and 28 pneumonectomies. They concluded that CT predicted FEV₁ reserves at 3–4 months after surgery more accurately than segmental counting or perfusion scintigraphy. Bolliger *et al.* (5) compared the ppo values of FEV₁, FVC, DLCO, and $\dot{V}O_2$ and measured the po values at 6 months after surgery for 30 lobectomies, 4 wedge resections, and 10 pneumonectomies, while the ppo values of each were estimated by quantitative CT, perfusion scintigraphy, number of segments, number of functional segments, and number of subsegments. They concluded that both perfusion scintigraphy and quantitative CT were useful irrespective of the resection, but perfusion scintigraphy-based results were the most accurate.

Table 6 ppo%DLCO, mean differences between the ppo and po values at 3 and 12 months after lobectomy and the limit of agreement

Method of estimation	ppo%DLCO (%)	Mean difference with po%DLCO (%), 3M	Limit of agreement -2SD, 2SD (%)	Determination coefficient	Mean difference with po%DLCO (%), 12M	Limit of agreement -2SD, 2SD (%)	Determination coefficient
RUL							
S	98.7±25.2	-1.3±12.8	-26.92, 24.23	R ² =0.68; P<0.01	7.5±12.9	-18.26, 33.34	R ² =0.72; P<0.01
Q	96.8±23.2	0.6±10.9	-21.30, 22.45	R ² =0.69; P<0.01	9.5±12.1	-14.81, 33.73	R ² =0.74; P<0.01
CT	92.4±22.1	5.0±9.1	-13.10, 23.16	R ² =0.77; P<0.01	13.9±11.2	-8.43, 36.25	R ² =0.80; P<0.01
CT _{LAV}	93.3±22.5	4.0±9.7	-15.44, 23.52	R ² =0.77; P<0.01	12.9±11.2	-9.39, 35.25	R ² =0.81; P<0.01
RLL							
S	90.2±23.4	8.5±15.4	-22.29, 39.34	R ² =0.43; P<0.01	14.1±18.0	-21.83, 49.99	R ² =0.58; P<0.01
Q	90.3±23	8.4±16.3	-24.33, 41.02	R ² =0.38; P<0.01	13.9±18.7	-23.56, 51.37	R ² =0.58; P<0.01
CT	95.4±23.9	3.3±18.3	-33.36, 39.92	R ² =0.29; P=0.02	8.8±20	-31.21, 48.89	R ² =0.48; P<0.01
CT _{LAV}	95.9±23.9	2.8±17.9	-32.97, 38.62	R ² =0.28; P=0.02	8.4±19.8	-31.30, 48.07	R ² =0.47; P<0.01
LUL							
S	82.4±18.4	2.5±11.6	-20.77, 25.71	R ² =0.66; P<0.01	12.1±12.8	-13.40, 37.62	R ² =0.54; P<0.01
Q	81.3±18.6	3.6±11.3	-19.11, 26.22	R ² =0.72; P<0.01	13.2±12.2	-11.18, 37.58	R ² =0.60; P<0.01
CT	78.2±18.8	6.7±13.7	-18.33, 32.82	R ² =0.51; P<0.01	16.3±14	-9.55, 43.33	R ² =0.50; P<0.01
CT _{LAV}	79.2±18.5	5.6±13.6	-19.39, 31.72	R ² =0.51; P<0.01	15.3±13.9	-10.56, 42.17	R ² =0.50; P<0.01
LLL							
S	91.3±18.2	-2.7±13.8	-30.31, 25.00	R ² =0.61; P<0.01	2.5±10.6	-18.67, 23.64	R ² =0.69; P<0.01
Q	90.3±18.3	-1.7±15	-31.63, 28.15	R ² =0.61; P<0.01	3.4±11.9	-20.45, 27.26	R ² =0.69; P<0.01
CT	91.6±18.6	-3.0±15.3	-32.16, 24.92	R ² =0.61; P<0.01	2.2±10.7	-21.62, 24.67	R ² =0.69; P<0.01
CT _{LAV}	91.8±18.5	-3.2±13.5	-32.24, 24.47	R ² =0.61; P<0.01	1.9±10.6	-21.70, 24.22	R ² =0.69; P<0.01

Values are represented as mean ± SD. RUL, right upper lobectomy; RLL, right lower lobectomy; LUL, left upper lobectomy; LLL, left lower lobectomy. COPD, chronic obstructive pulmonary disease; %DLCO, percent predicted lung diffusion capacity for carbon monoxide; LAV, low-attenuation volume; Limit of agreement, mean ± 2 SD; M, months; po, postoperative value; ppo, predicted postoperative value.

Anatomically based calculations should be reserved for resections not exceeding one lobe. Fourdrain *et al.* (3) compared a quantitative CT based ppoFEV₁, excluding emphysematous lesions, using 19-segment perfusion and ventilation scintigraphy, the Nakahara formula (25), and the Juhl & Frost formula (26) based on preoperative spirometry for 23 patients undergoing surgical resection of non-small cell lung cancer (NSCLC), including 18 single and bi-lobectomies and 5 pneumonectomies. Quantitative CT showed that the mean volume difference of FEV₁ between pre-operation and 12 months after surgery was 266±229 mL, and the highest R² (=0.79) compared to the other estimation methods. In contrast, Win *et al.* (6)

compared ppoFEV₁ estimated by the number of segments and perfusion and ventilation scintigraphy preoperatively and at 18 months after surgery for 61 NSCLC patients undergoing surgical resection, including 56 single lobectomies. They concluded that quantitative ventilation-perfusion scintigraphy was not necessary in the preoperative assessment of lung cancer patients undergoing lobectomy.

However, many of these previous studies did not consider whether patients were diagnosed with COPD. The present study suggests that S seems to be a better technique to calculate ppoFEV₁ and ppo%DLCO than the other three techniques for single lobectomy when patients were classified into non-COPD and COPD.

Comparison between the resected lobes

Interestingly, the estimation technique that showed the smallest mean difference between ppo and actual postoperative values for FEV₁ and %DLCO were different according to the resected lobe in our study.

At 3 months after lobectomy, the estimation technique that showed the smallest mean differences was Q for RUL, CT and CT_{LAV} for RLL, and S for LUL for both FEV₁ and %DLCO. For LLL, all four techniques provided overestimated ppo values compared to the poFEV₁ and po%DLCO. At 12 months after lobectomy, those overestimations disappeared for LLL, and CT and CT_{LAV} showed the smallest mean differences for both lower lobectomies (LLL and RLL).

The actual po values for FEV₁ at 12 months remained smaller than the ppo values calculated by S for RUL. When the volume of each pulmonary lobe was divided by the number of segmental bronchi, RUL occupied the largest segmental volume compared to the other lobes (0.31±0.1 L). The reason may be that S overestimated the ppo value for RUL.

The smallest mean differences were shown by Q followed by CT_{LAV} for RUL. Obtaining CT imaging is necessary to evaluate lung disease before surgery, but scintigraphy is not. Prediction of postoperative values estimated by quantitative CT, especially with LAV calculation (CT_{LAV}), may be better than Q even for RUL, because patients sometimes do not agree to more radiation exposure by scintigraphy, and/or due to the lack of scintigrams in the hospital. Win *et al.* (6) concluded that scintigraphy should be used for further evaluation in patients with quantitative CT predicted FEV₁ in the range of 40% predicted or lower.

For both FEV₁ and %DLCO, CT_{LAV} showed larger ppo values than CT, and CT_{LAV} showed smaller mean difference values than CT in both non-COPD and COPD groups, and for any area of lobe resection. In this study, CT_{LAV} showed the smallest mean differences for LLL and RLL at 12 months after lobectomy, with smaller %LAV values than the upper lobes (Table 4). When pulmonary emphysema progresses, airflow limitation increases, and the alveolar gas exchange area decreases because the alveolar wall is destroyed, thus reducing FEV₁ and DLCO. In this study, LAV impacted the upper lobes more than the lower lobes (27). RUL and LUL retained two lower lobes with a smaller LAV and one upper lobe with a larger LAV. Subsequently, the upper lobe lobectomy can lose

the “worse” lobe, which has increased flow limitation and increased amount of destroyed pulmonary capillary bed, improving their FEV₁ and DLCO with expansion and pulmonary capillary recruitment and distension of the remaining “better” lobes (12). This postoperative improvement of pulmonary function may be overlapping the ppo values estimated by volume-based CT and CT_{LAV} technique. In contrast, RLL and LLL retain one “better” lower lobe with smaller LAV and two “worse” upper lobes with larger LAV. In such cases, CT-based techniques may be adequate for estimating ppo values, because flow limitation and diffusion capacity do not improve excessively in lower lobe lobectomy (12).

The present study suggests that CT_{LAV} is a better technique to calculate ppoFEV₁ and ppo%DLCO when patients are classified on the basis of the resected lobe. In addition, in case of patients with maldistribution of the lung’s blood flow, Q seems better than CT_{LAV} because CT images show lung volume well, but they do not indicate pulmonary function as Q does.

Study limitations

Firstly, the number of patients per lobectomy location was small. The total number of VATS lobectomy has been increasing, but it was not easy to match the number of resected lobes and the number of patients who are diagnosed as non-COPD or COPD using the GOLD classification (16). The current study described the effect of COPD and anatomical location on the ppo values, and a further study with a larger sample size may clarify this effect for the ppo calculation. Secondly, there were no high-risk patients for perioperative mortality (1,2) in this study. Further research is needed to elucidate the relationship between estimation methods and postoperative values according to the resected lobe, complications, or mortality after pulmonary resection in patients with preoperatively lower pulmonary function.

Conclusions

S appears to be an adequate method for estimating ppoFEV₁ and ppo%DLCO, when patients are classified into non-COPD and COPD groups. However, S sometimes overestimates the ppo values when patients are classified on the basis of the resected lobe. Using an individual estimating method may be necessary for evaluating ppo values associated with the location of the lobe that will be

resected. The CT_{LAV} method may be the method of choice instead of S for calculating $ppoFEV_1$ and $ppo\%DLCO$ in patients who undergo lobectomy despite the presence or absence of airflow limitation.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Kitasato University Medical Ethics Organization on June 28, 2013 (approval KME0 B13-110) and written informed consent was taken from all the patients.

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