Correlation between quantitative computed tomography analysis and pulmonary function in children with post-infectious bronchiolitis obliterans

Jonghyeon Kim

Department of Medicine

The Graduate School, Yonsei University

Correlation between quantitative computed tomography analysis and pulmonary function in children with post-infectious bronchiolitis obliterans

Directed by Professor Mi-Jung Lee

The Master's Thesis
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medical Science

Jonghyeon Kim

June 2017

This certifies that the Master's Thesis of Jonghyeon Kim is approved.

Thesis Supervisor : Mi-Jung Lee

Thesis Committee Member#1 : Myung-Joon Kim

Thesis Committee Member#2 : Kyung Won Kim

The Graduate School
Yonsei University

June 2017

ACKNOWLEDGEMENTS

First and foremost I express my gratitude to my supervisor, Professor Mi-Jung Lee, who has sincerely guided and supported me throughout my thesis. Without her support, this work would not have been completed.

Furthermore I would like to thank Professor Myung-Joon Kim and Kyung Won Kim, for sparing me their valuable time to help complete this thesis

Professor Hyun Joo Shin and Dr. Haesung Yoon also offered precious comments during writing of the thesis and deserves my sincere gratitude.

I also would like to thank Dong-Su Jang, MFA, (Medical Illustrator) for his help with the illustrations.

Finally, I appreciate my family for everlasting trust and support, which deserve my sincere gratitude.

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Correlation between quantitative computed tomography analysis and pulmonary function in children with post-infectious bronchiolitis obliterans

Jonghyeon Kim

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Mi-Jung Lee)

Purpose: To investigate the availability of computed tomography (CT) based quantitative airway and emphysema measurements and to assess their correlation with pulmonary function in children with post-infectious bronchiolitis obliterans (PIBO).

Materials and Methods: This retrospective study included chest CT scans and pulmonary function tests (PFT) completed between January 2005 and December 2016 on children diagnosed with PIBO. The quantitative analysis of segmental and subsegmental bronchi was performed on each chest CT scan. The emphysema volume (EV), the volume of lung area exhibiting lower attenuation than the mean attenuation of normal and air trapping areas, was also measured in each lobe. The ratio between EV and total lung volume (emphysema ratio, ER) was then calculated. The PFT values included spirometric parameters and impulse oscillometric parameters. Comparison analyses between CT parameters and PFT results were made with Pearson or Spearman.

Results: In total 23 patients were enrolled (age 7.0 ± 3.3 years – range, 4-15 years). We successfully measured 371 (371/414, 89.6%) segmental and 242 (242/414, 58.5%) subsegmental bronchi. In airway analysis, wall area showed negative correlation with forced expiratory volume in one second (FEV_1) in the majority of the pulmonary lobes. The airway average diameter and airway area were also negatively correlated with FEV_1 in bilateral lower lobes. Emphysema analyses demonstrated that EV was negatively correlated with FEV_1 and positively correlated with an oscillometric parameter, reactance at 5 Hz.

Conclusion: Quantitative airway and emphysema measurements from chest CT are feasible and can demonstrate pulmonary function in pediatric PIBO patients.

.

Key words : lung, computed tomography, pulmonary function test, bronchiolitis obliterans, child, quantitative imaging

Correlation between quantitative computed tomography analysis and pulmonary function in children with post-infectious bronchiolitis obliterans

Jonghyeon Kim

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Mi-Jung Lee)

I. INTRODUCTION

Post-infectious bronchiolitis obliterans (PIBO) is a rare but potentially irreversible and highly morbid chronic obstructive lung disease that results from a severe lower respiratory tract infection in children. Histopathological features of PIBO include concentric narrowing and obliteration of small airways due to an inflammatory process surrounding the bronchiolar lumen[1].

Signs, symptoms and prognosis of PIBO vary. Confirmative diagnosis of PIBO requires histopathological examination, but it is invasive and challenging due to patient's clinical instability and the heterogeneous distribution of lesions. Therefore, in actual practice, the diagnosis is often made based on clinical features and computed tomography (CT) findings. The severity of disease and its clinical course are monitored by pulmonary function test (PFT)[2]. However, the reliability of PFT is variably affected by patient's compliance and sometimes it is difficult to check pulmonary function in young patients[3].

On the other hand, CT is relatively easier to be performed in young patients and provides stable and reliable results. Although conventional CT cannot directly delineate small airways, it does reveals secondary findings that are caused by obstruction of small airways. The characteristic CT features of PIBO include a mosaic air trapping pattern, bronchiectasis and atelectasis with heterogeneous distribution throughout the entire lung[2,4]. The greatest disadvantage of using CT scans with pediatric patients is the radiation exposure. It remains, however, the fastest and easiest method for evaluating the whole lung, and recently a low dose CT protocol has been developed that nonetheless results in acceptable image quality by using iterative reconstruction[5].

Quantitative imaging analysis provides an additional promising application of CT for evaluating small airway disease by directly measuring the airway and indirectly quantifying the degree of air trapping (or emphysema). Several studies of adult chronic obstructive pulmonary disease (COPD) and asthma patients have shown that quantitative CT measurements are significantly correlated with PFT results[6-9]. However, there have only been a few studies that utilized the semi-quantitative measurements of CT findings[4,10] or quantitatively assessed the degree of air trapping based on CT scans[11] performed in children. Moreover, there have been no dedicated studies that have applied quantitative airway analysis on CT data for pediatric patients. Recently, with technical improvement, quantitative CT airway measurement in children has also become available in spite of lower spatial resolution. As a result, this study aims to investigate the availability of CT based quantitative airway and emphysema measurements and their correlation with the results of PFT in children with PIBO.

II. MATERIALS AND METHODS

1. Patients

This retrospective study was approved by the relevant institutional review board, and the requirement for written informed consent was waived. We searched our institutional database for patients diagnosed with PIBO who were under 15 years of age and that had previously undergone both a chest CT scan and PFT within a one-month interval at some point between January 2005 and December 2016. Patients with a history of malignancy or organ transplantation, as well as those with active pneumonia during their chest CT scan, were excluded.

2. Chest CT scan

Chest CT scans were performed with one of five CT systems (Sensation 16, Sensation 64, Somatom Definition AS+, and Somatom Definition Flash from Siemens Medical Solutions, Erlangen, Germany; and Discovery CT 750 HD from GE Healthcare, Waukesha WI, USA). Tube voltages ranging from 70 to 140 kVp were chosen based on the patient's weight. Automatic dose modulation technique was applied, if possible. Each patient was moved into a supine position, encouraged to inhale deeply and to hold their breath during the examination, if possible. For children under eight years of age, sedation was performed under the supervision of pediatric anesthesiologists.

All volume CT dose indices (CTDIvol) and dose length product values were recorded, from which we calculated CTDIvol in terms of size-specific dose estimates (SSDE) with reference to the American Association of Physicists in Medicine report 204[12]. Effective radiation doses were estimated by multiplying dose length product by age-specific conversion factors[13]. We also verified the use of iodine contrast.

3. Quantitative CT scan analyses

CT scans were quantitatively analyzed using dedicated imaging analysis software (Intellispace Portal, version 7.0, Philips Medical Systems, Cleveland, OH, USA). Both airway and emphysema parameters were determined following analyses protocol outlined below.

A. Airway measurement

First, automatic segmentation of the airways was done using the relevant software followed by manual modification in order to include the most distal branches. After the segmentation, a representative branch from each segment was selected. Specifically, the left segment 1+2 and segment 7+8 were each counted as a single segment. As such, a maximum 18 segmental and subsegmental bronchi could be identified per patient. The start point and the end point of each segmental and subsegmental bronchus were marked by a radiologist on either volume-rendered or cross-sectional images. We subsequently used the relevant software to measure and calculate the following for each segmental and subsegmental bronchus: wall thickness (WT), wall area (WA), lumen average diameter (LAD), lumen area (LA), WA/LA ratio, airway average diameter (AAD), and airway area (AA) (Figure 1). For simplification, all segmental and subsegmental bronchi were grouped according to the pulmonary lobe in which they are physically located, and the mean value for each parameter was calculated across all bronchi within each lobe, grouped as follows: right segment 1-3 (referred to as right upper lobe, or RUL), right segment 4 and 5 (referred to as right middle lobe, or RML), right segment 6-10 (referred to as right lower lobe, or RLL), left segment 1-5 (referred to as left upper lobe, or LUL), and left segment 6-10 (referred to as left lower lobe, or LLL).

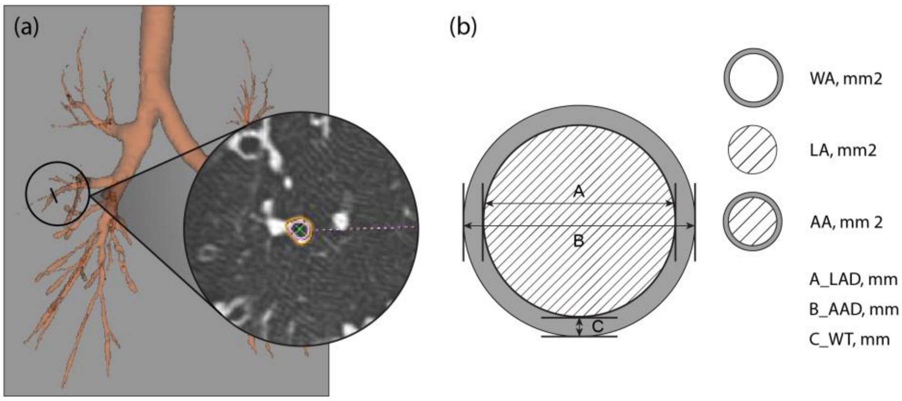

Figure 1. Schematic drawing of airway parameters.

Abbreviations: WA, wall area; LA, lumen area; AA, airway area, LAD, lumen average diameter; AAD, airway average diameter; WT, wall thickness

B. Emphysema assessment

Measurements of emphysema were performed using the previously published individualized threshold protocol[11]. Two small regions of interest (ROIs) were identified on the axial images from each chest CT, which were located in the most representative areas from both normal and air-trapping parenchyma. The lung's dependent area was avoided as its attenuation value could be inappropriately exaggerated. The mean CT attenuation values for each defined ROI were measured, and the average of the two attenuation values was used as the threshold for distinguishing the emphysema area from the normal lung parenchyma. We used the relevant software to measure the emphysema volume (EV), which was defined as the lung volume when the attenuation level is below the established threshold. Each patient's total lung volume was also measured and the emphysema ratio (ER) was calculated as the ratio between EV and total lung volume. All measurements were also performed on the pulmonary lobes.

4. Analysis of PFT

We included PFTs that were completed within one month of the associated chest CT scan. All tests were performed according to the American Thoracic Society (ATS) criteria[14] using the Jaeger MasterScreen PFT system (Jaeger Co, Wurzberg, Germany). Both spirometry and impulse oscillometry studies were included as components of the test. Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF) and forced expiratory flow at 25–75% of the pulmonary volume ($FEF_{25\text{-}75}$) were measured before and after bronchodilator inhalation. The impulse oscillometry study measured the following parameters before and after bronchodilator inhalation: respiratory resistance, respiratory reactance, and reactance area at a frequency ranging from 5 to 20 Hz. All data are expressed as the percentage of the predicted reference values.

5. Statistical analyses

Statistical analyses were completed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp. Armonk, NY, USA). The Kolmogorov-Smirnov test was used to assess the normality of each dataset, and the correlation between CT measurements and PFT results was assessed using either the Pearson or Spearman correlation, depending on the normality of the variables. In order to analyze the airway parameters, we included the mean value for each segmental bronchus found in each lung (right and left) and lobe (RUL, RML, RLL, LUL, and LLL). The same process was used to assess the same set of airway parameters in subsegmental bronchi. For emphysema parameters, either the Pearson or Spearman correlation analysis was used as outlined above. P-values less than 0.05 were defined as statistically significant.

III. RESULTS

1. Patients' characteristics and CT radiation dose

This study included 23 patients receiving a total of 23 CT scans. They all were diagnosed with PIBO by conventional CT. This study population comprised 10 boys and 13 girls, with a mean age at the time of CT scan of 7.0 ± 3.3 years (ranging from 4 to 15 years). The ranges for height, weight, and body mass index were 99-169 cm, 14-67 kg, and 13.6-24.0 kg/m^2, respectively.

CT scans used the following tube voltages: two scans at 70 kVp, 12 scans at 80 kVp, six scans at 100 kVp, two scans at 120 kVp, and one scan at 140 kVp. Sixteen of the 23 CT scans also included an intravenous contrast injection. SSDE was determined to be 16.3 ± 28.6 mGy (range, 1.3 - 133.9 mGy), the dose length product was 158.4 ± 256.0 mGy-cm (range, 16 – 978 mGy-cm), and the effective dose was 2.2 ± 3.3 mSv (range, 0.3 – 12.7 mSv), across all patients.

2. Quantitative CT scan analyses

All the relevant airway measurements for each pulmonary lobe and emphysema assessment results are summarized in Table 1. Airway measurements were successfully completed for a total of 371 out of 414 segmental bronchi (89.6%) and 242 out of 414 subsegmental bronchi (58.5%). The proportions of segmental bronchi analyzed for each lobe region were as follows: 66 (66/69, 95.7%) for the RUL, 39 (39/46, 84.8%) for the RML, 99 (99/115, 86.1%) for the RLL, 84 (84/92, 91.3%) for the LUL, and 83 (83/92, 90.2%) for the LLL. Of the five youngest patients (each 4 years of age), we successfully analyzed all the segmental bronchi in three patients (Figure 2). Failed airway segmentation in the other cases were due to atelectasis (n=4, Figure 3), bronchiectasis (n=1), mucus impaction (n=1), and a motion artifact (n=1). All the relevant airway measurements in each pulmonary lobe are summarized in Table 1. Briefly, WT, LAD and AAD were 1.4 ± 0.3 mm, 2.9 ± 0.8 mm and 5.7 ± 0.9 mm, respectively, in the right lung, and were equal to 1.3 ± 0.4 mm, 2.8 ± 0.8 mm and 5.5 ± 1.1 mm, respectively, in the left lung. WA, LA and AA were 20.2 ± 5.8 mm^2, 7.4 ± 4.1 mm^2 and 27.7 ± 8.3 mm^2, respectively, in the right lung and 18.6 ± 7.5 mm^2, 7.4 ± 4.7 mm^2 and 26.0 ± 10.3 mm^2, respectively in the left lung.

Emphysema assessments were successfully performed during all 23 CT scans. The mean attenuation value was -760 ± 92 HU in normal lung parenchyma and -851 ± 67 HU in air-trapping lung parenchyma. The threshold for defining emphysema, therefore, was established at -806 ± 75 HU. EV and ER measurements from each pulmonary lobe are summarized in Table 1. Briefly, EV and ER were determined to be 195.5 ± 323.5 cc and 22.1 ± 16.8%, respectively, in the right lung and 196.1 ± 311.8 cc and 26.3 ± 18.9%, respectively, in the left lung.

Table 1. Quantitative CT airway and emphysema parameters measured in 23 post-infectious bronchiolitis obliterans patients

	Airway parameters							Emphysema parameters	
	WT (mm)	WA (mm^2)	LAD (mm)	LA (mm^2)	WA/LA ratio (%)	AAD (mm)	AA (mm^2)	EV (cc)	ER (%)
Right lung	1.4 ± 0.3	20.2 ± 5.8	2.9 ± 0.8	7.4 ± 4.1	363.7 ± 171.6	5.7 ± 0.9	27.7 ± 8.3	195.5 ± 323.5	22.1 ± 16.8
RUL	1.4 ± 0.3	20.4 ± 6.5	2.9 ± 0.8	7.4 ± 4.1	368.1 ± 186.2	5.8 ± 1.0	27.8 ± 8.7	63.4 ± 121.8	18.1 ± 14.6
RML	1.4 ± 0.3	20.0 ± 7.3	2.9 ± 1.2	7.8 ± 6.9	371.5 ± 200.3	5.7 ± 1.3	27.8 ± 12.6	41.2 ± 39.1	35.7 ± 20.0
RLL	1.4 ± 0.3	19.3 ± 6.0	2.8 ± 0.5	6.6 ± 2.4	355.3 ± 151.6	5.6 ± 0.8	25.9 ± 7.2	91.0 ± 170.3	20.9 ± 19.8
Left lung	1.3 ± 0.4	18.6 ± 7.5	2.8 ± 0.8	7.4 ± 4.7	336.9 ± 180.8	5.5 ± 1.1	26.0 ± 10.3	196.1 ± 311.8	26.3 ± 18.9
LUL	1.3 ± 0.4	16.9 ± 7.2	2.6 ± 0.9	6.4 ± 4.8	362.3 ± 227.7	5.2 ± 1.1	23.3 ± 10.0	84.2 ± 127.3	23.7 ± 17.1
LLL	1.4 ± 0.4	21.3 ± 8.9	3.1 ± 0.9	8.6 ± 5.4	323.7 ± 153.9	5.9 ± 1.2	29.9 ± 12.0	111.8 ± 193.7	27.6 ± 23.2

Abbreviations: RUL, right upper lobe; RML right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; WT, wall thickness; WA, wall area; LAD, lumen average diameter; LA, lumen area; AAD, airway average diameter; AA, airway area; EV, emphysema volume; ER, emphysema ratio

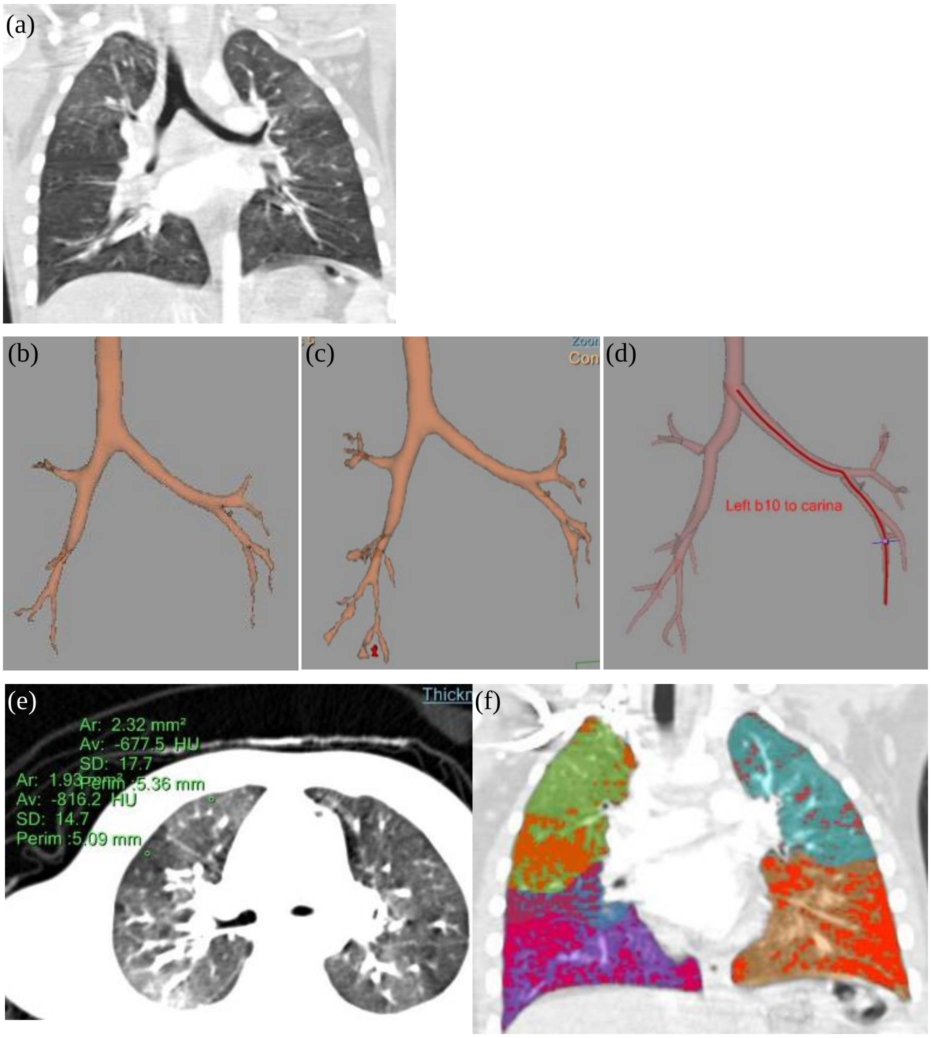

Figure 2. A representative case of a successful quantitative analysis in a four-year-old girl with post-infectious bronchiolitis obliterans. (a) The coronal reconstructed CT image demonstrates bronchial wall thickening with mosaic attenuation in bilateral lungs. (b and c) Automatic airway segmentation (b) and subsequent manual editing (c) reveals all segmental bronchi in bilateral lungs. (d) Each segment is labeled. (e) Small regions of interest are drawn at normal and air-trapping lung parenchyma to calculate individualized threshold value of emphysema. (f) Lung parenchyma area with CT attenuation value lower than the calculated threshold is masked with orange color.

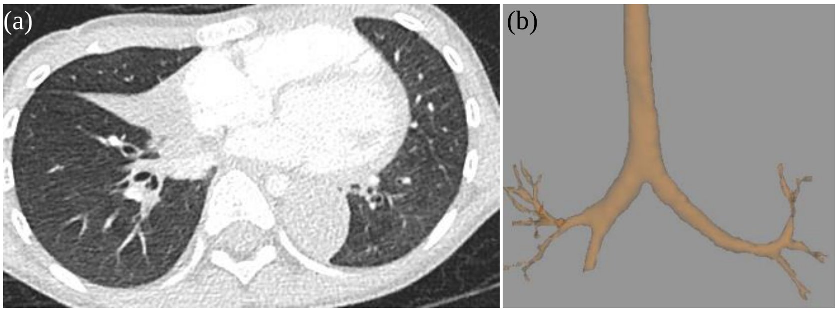

Figure 3. A representative case showing the failure of quantitative airway analysis in a four-year-old boy with post-infectious bronchiolitis obliterans. (a) An axial CT image shows atelectasis of right middle lobe and left lower lobe. Airways are not delineable in the affected areas. (b) Airway segmentation failed in the corresponding and distal regions.

3. PFT results

All 23 PFTs were deemed acceptable and reproducible, according to the ATS criteria. The time interval between each CT scan and its associated PFT was 6.6 ± 8.5 days with (ranging from 0-33 days). FEV_1 values (% predicted) measured before and after bronchodilator inhalation were 81.5 ± 25.0% and 86.6 ± 25.7%, respectively. The median change in FEV_1 was 3.2% with the interquartile range of 0.8-17.3%. Thirteen patients (13/23, 56.5%) were found to have FEV_1 value higher than 80%. All spirometry and impulse oscillometry measurements are provided in Supplemental Table 1.

4. Correlation between airway CT parameters and PFT results

While we found that the precise results from our correlation tests varied slightly between pulmonary lobes in each patient, we nonetheless found that WA exhibited a significant negative correlation with pre-bronchodilator FEV_1 in both lungs (ρ = -0.481, p = 0.024 in the right lung and ρ = -0.452, p = 0.034 in the left lung) (Table 2). When the parameters were grouped by pulmonary lobe, we found that the parameters exhibiting significant correlation with FEV_1 varied in each lobe, as follows: WA correlates in the RUL, WT correlates in the RML, WT, WA, AAD, and AA correlate in the RLL, WT and WA correlate in the LUL, and WA, AAD and AA correlate in the LLL (all $p < 0.05$) (Table 2). A similar tendency of correlation toward airway parameters was found with PEF and post-bronchodilator FEV_1 in each pulmonary lobe (Supplemental Table 2). The impulse oscillometry study, however, revealed no significant correlation with any airway parameters in any of the pulmonary lobes.

In the subsegmental bronchi, we identified a similar correlation between airway parameters and PFT, with WA demonstrating a significant negative correlation with pre-bronchodilator FEV_1 in both lungs ($\rho = -0.632$, $p = 0.006$ in right lung and $\rho = -0.577$, $p = 0.015$ in left lung), as well as the majority of the pulmonary lobes (Supplemental Table 3).

5. Correlation between emphysema CT parameters and PFT results

Of the two emphysema-related CT parameters, only EV was found to have a significant negative correlation with pre- and post-bronchodilator FEV_1, as well as a positive correlation with the impulse oscillometeric parameter (respiratory reactance at 5Hz) in the majority of pulmonary lobes with the exception of the RML (Supplemental Table 4). We found the relevant correlation coefficient (ρ) between EV and pre- and post-bronchodilator FEV_1 to be -0.472 ($p = 0.023$) and -0.474 ($p = 0.022$) in the right lung and -0.571 ($p = 0.004$) and -0.571 ($p = 0.004$) in the left lung (Table 2).

Table 2. Correlation between airway or emphysema parameters and pre-bronchodilator FEV_1

	Airway parameters														Emphysema parameters			
	WT		WA		LAD		LA		WA/LA ratio		AAD		AA		EV		ER	
	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value
Right lung	**-0.456**	**0.033**	**-0.481**	**0.024**	-0.048	0.831	-0.044	0.845	-0.195	0.384	-0.336	0.127	-0.357	0.102	**-0.472**	**0.023**	-0.219	0.315
RUL	-0.414	0.055	**-0.490**	**0.021**	-0.101	0.656	-0.067	0.765	-0.041	0.858	-0.379	0.082	-0.396	0.068	**-0.499**	**0.015**	-0.327	0.128
RML	**-0.486**	**0.030**	-0.440	0.052	-0.012	0.959	0.000	0.999	-0.270	0.250	-0.264	0.261	-0.255	0.278	-0.274	0.206	0.158	0.473
RLL	**-0.462**	**0.035**	**-0.512**	**0.018**	-0.172	0.457	-0.192	0.405	-0.156	0.501	**-0.449**	**0.041**	**-0.490**	**0.024**	**-0.478**	**0.021**	-0.273	0.207
Left lung	-0.384	0.078	**-0.452**	**0.034**	-0.156	0.488	-0.217	0.332	-0.226	0.312	-0.389	0.073	**-0.432**	**0.045**	**-0.571**	**0.004**	-0.396	0.061
LUL	**-0.430**	**0.046**	**-0.486**	**0.022**	-0.056	0.804	-0.089	0.692	-0.283	0.202	-0.350	0.110	-0.394	0.069	**-0.443**	**0.034**	-0.071	0.747
LLL	-0.384	0.078	**-0.453**	**0.034**	-0.235	0.292	-0.295	0.183	-0.173	0.443	**-0.437**	**0.042**	**-0.471**	**0.027**	**-0.628**	**0.001**	-0.478	0.021

Note: Statistically significant values ($p < 0.05$) are marked in bold.

Abbreviations: RUL, right upper lobe; RML right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; WT, wall thickness; WA, wall area; LAD, lumen average diameter; LA, lumen area; AAD, airway average diameter; AA, airway area; EV, emphysema volume; ER, emphysema ratio

IV. DISCUSSION

This study has demonstrated that it was technically feasible to obtain quantitative measurements of segmental airways using CT scans in children, even in preschoolers, and further, it has shown that this application holds potential clinical value for assessing PIBO patients. For adult patients, quantitative airway analyses of CT scans have been widely examined and it has been found to hold significant clinical applications in ever-smokers[15] and COPD patients with pulmonary hypertension[16]. By contrast, there has to date been no detailed study of children with quantitatively analyzed segmental airways based on CT data. Some degree of assessment has been provided by Mattiello et al.[4], in which the authors used the modified Bhalla score[17,18] in order to analyze CT findings from PIBO patients in a semi-quantitative way, from which they concluded that CT-based scores assessed in young patients successfully predict each patient’s level of future lung function. Similarly, Yoon et al.[10] assessed the bronchial wall thickness in PIBO patients and compared it with the state of the adjacent pulmonary artery, which was assessed as being either absent (invisible or as thin as pencil drawing), mild (half or less than half of the adjacent pulmonary artery diameter), or severe (more than half of the adjacent pulmonary artery diameter). This study found that bronchial wall thickening was the only CT feature that differed significantly between patients that were responsive to intravenous pulse methylprednisolone therapy, and those that were unresponsive to that therapy. Although these studies were limited in that they were not strictly quantitative, their conclusions do strongly suggest that the use of CT scan data in PIBO patients is likely to have substantial clinical relevance.Our study is the first report to evaluate quantitative chest CT assessment including airway measurements in children and demonstrated potential clinical value for assessing PIBO patients using this method.

In the present study, CT-based quantitative airway measurements were successfully completed for 89.6% of all segmental bronchi across all patients, suggesting that a reasonable degree of quantitative segmental bronchi analysis can be completed in children. The success rate for subsegmental bronchi, however, was only 58.5%, suggesting that these methods are not as effective at resolving particularly small bronchial regions while maintaining their low radiation dose. We argue, however, that even with the reduced spatial resolution in pediatric chest CT, these results are sufficient to support their clinical application.

In assessment of correlation between airway measurements and PFT results, we identified a significant negative correlation between WA and FEV_1 in the majority of the pulmonary lobes. FEV_1 is known as the most reproducible parameter that reflects the severity of obstructive lung disease, and its value decreases under conditions of increasing pathological symptoms. Thus, it can be interpreted that the WA becomes wider as the degree of disease increases. This seems to be consistent with one of the primary features of PIBO pathology, which is the inflammation surrounding the airway lumen[1], a feature that appears as a widened WA on cross-sectional images. We found that the degree of correlation, however, varied depending on the lobe being examined, and that there was no correlation between WA and EV in the RML. PIBO is able to produce a highly heterogeneous distribution of severity across the lung regions, suggesting that the variable degree of correlation between CT-based measurements and PFT results for each lobe likely reflects the true heterogeneity of the disease.

Quantitative chest CT analysis also included emphysema assessment, and there are several studies that have examined its clinical utility for adult patients. There are two critical differences between adults and children, however, those should be taken into account when measuring EV. First, the degree of CT attenuation in normal lungs changes depending on the patient's age in children[19]; second, respiratory control is often difficult to realize for children.

With this study, we applied the individualized threshold method originally established by Kim et al.[11] to measure EV in PIBO patients, and our analyses identified a significant negative correlation between EV and FEV_1 in both lungs and in the majority of lobes, which is consistent with our WA measurement results. This finding is consistent with the known PIBO pathophysiology, which states that the greater the trapped air volume, the greater the severity of the disease. We expected that EV measurements would have practical advantages, as it requires less time and effort than a complete airway analysis. We found that EV was also correlated with an impulse oscillometric parameter (reactance at 5 Hz). Parameters measured by impulse oscillometry have been shown to reflect the small airways in the lung periphery[20]. For example, previous work reported that impedance, resistance and reactance (at 5 Hz) are unusually high in PIBO patients[21]. Overall, our results are consistent with this previous study, and it suggests that EV may better reflect the true condition of small airways.

The present study does have some limitations. First, we examined only a small number of patients (23 in total), as we required there be only a short amount of time separating CT and PFT in order to increase the validity of the correlation analysis. Second, this was a retrospective study that examined previously collected data, making it vulnerable to potential selection bias, as well as to inconsistent CT scan protocols that may affect spatial resolution or alter the capability of airway segmentation. The respiratory phase was not fixed, which can affect attenuation value of the lung parenchyma, as well as other airway parameters, which is unfortunately unavoidable in performing CT scans on children. Third, this study lacks longitudinal follow-up data. PFT does not precisely indicate disease severity, and as such, identifying a measurement that correlates well with the clinical outcome would provide a better demonstration of the benefit of using quantitative analysis in these patients. Despite these limitations, this study provides meaningful evidence that the quantitative CT analysis of pediatric PIBO patients can be leveraged for more effective diagnosis and monitoring. We suggest that future research should be undertaken with a larger sample size and while also measuring long-term clinical outcomes.

V. CONCLUSION

In conclusion, we found that effective quantitative airway measurements and emphysema assessments based on chest CT of young children are technically feasible, and that some of their metrics are correlated with pulmonary function parameters in pediatric PIBO patients, specifically measurements of WA in the airway and EV in emphysema. Quantitative CT analysis could be used for clinical applications in order to estimate the disease severity in children with PIBO, whose PFT cannot be checked due to limited compliance.

REFERENCES

1. Mauad T, Dolhnikoff M. Histology of childhood bronchiolitis obliterans. Pediatr Pulmonol 2002;33:466-74.
2. Fischer GB, Sarria EE, Mattiello R, Mocelin HT, Castro-Rodriguez JA. Post infectious bronchiolitis obliterans in children. Paediatr Respir Rev 2010;11:233-9.
3. Loeb JS, Blower WC, Feldstein JF, Koch BA, Munlin AL, Hardie WD. Acceptability and repeatability of spirometry in children using updated ATS/ERS criteria. Pediatr Pulmonol 2008;43:1020-4.
4. Mattiello R, Sarria EE, Mallol J, Fischer GB, Mocelin H, Bello R, et al. Post-infectious bronchiolitis obliterans: can CT scan findings at early age anticipate lung function? Pediatr Pulmonol 2010;45:315-9.
5. Yoon H, Kim MJ, Yoon CS, Choi J, Shin HJ, Kim HG, et al. Radiation dose and image quality in pediatric chest CT: effects of iterative reconstruction in normal weight and overweight children. Pediatr Radiol 2015;45:337-44.
6. Kauczor HU, Wielputz MO, Owsijewitsch M, Ley-Zaporozhan J. Computed tomographic imaging of the airways in COPD and asthma. J Thorac Imaging 2011;26:290-300.
7. Lederlin M, Laurent F, Portron Y, Ozier A, Cochet H, Berger P, et al. CT attenuation of the bronchial wall in patients with asthma: comparison with geometric parameters and correlation with function and histologic characteristics. AJR Am J Roentgenol 2012;199:1226-33.
8. Montaudon M, Lederlin M, Reich S, Begueret H, Tunon-de-Lara JM, Marthan R, et al. Bronchial measurements in patients with asthma: comparison of quantitative thin-section CT findings with those in healthy subjects and correlation with pathologic findings. Radiology 2009;253:844-53.
9. Orlandi I, Moroni C, Camiciottoli G, Bartolucci M, Pistolesi M, Villari N, et al. Chronic obstructive pulmonary disease: thin-section CT measurement of airway wall thickness and lung attenuation. Radiology 2005;234:604-10.
10. Yoon HM, Lee JS, Hwang JY, Cho YA, Yoon HK, Yu J, et al. Post-infectious bronchiolitis obliterans in children: CT features that predict responsiveness to pulse methylprednisolone. Br J Radiol 2015;88:20140478.
11. Kim HG, Shin HJ, Kim YH, Sohn MH, Lyu CJ, Kim MJ, et al. Quantitative computed tomography assessment of graft-versus-host disease-related bronchiolitis obliterans in children: A pilot feasibility study. Eur Radiol 2015;25:2931-6.
12. Boone JM, Strauss KJ, Cody DD, McCollough CH, McNitt-Gray MF, Toth TL. Size-specific dose estimates (SSDE) in pediatric and adult

body CT examinations. AAPM report: American Association of Physicists in Medicine; 2011.
13. McCollough C, Cody D, Edyvean S, Geise R, Gould B, Keat N, et al. The measurement, reporting and management of radiation dose in CT. AAPM report: American Association of Physicists in Medicine; 2008.
14. Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. Am Rev Respir Dis 1991;144:1202-18.
15. Johannessen A, Skorge TD, Bottai M, Grydeland TB, Nilsen RM, Coxson H, et al. Mortality by level of emphysema and airway wall thickness. Am J Respir Crit Care Med 2013;187:602-8.
16. Dournes G, Laurent F, Coste F, Dromer C, Blanchard E, Picard F, et al. Computed tomographic measurement of airway remodeling and emphysema in advanced chronic obstructive pulmonary disease. Correlation with pulmonary hypertension. Am J Respir Crit Care Med 2015;191:63-70.
17. Bhalla M, Turcios N, Aponte V, Jenkins M, Leitman BS, McCauley DI, et al. Cystic fibrosis: scoring system with thin-section CT. Radiology 1991;179:783-8.
18. Dodd JD, Barry SC, Barry RB, Gallagher CG, Skehan SJ, Masterson JB. Thin-section CT in patients with cystic fibrosis: correlation with peak exercise capacity and body mass index. Radiology 2006;240:236-45.
19. Stein JM, Walkup LL, Brody AS, Fleck RJ, Woods JC. Quantitative CT characterization of pediatric lung development using routine clinical imaging. Pediatr Radiol 2016; doi:10.1007/s00247-016-3686-8.
20. Bickel S, Popler J, Lesnick B, Eid N. Impulse oscillometry: interpretation and practical applications. Chest 2014;146:841-7.
21. Li YN, Liu L, Qiao HM, Cheng H, Cheng HJ. Post-infectious bronchiolitis obliterans in children: a review of 42 cases. BMC Pediatr 2014;14:238.

APPENDICES

Supplemental Table 1. Result of pulmonary function test in 23 patients diagnosed with post-infectious bronchiolitis obliterans

Spirometry	Mean or *median* [a]	SD or *IQR* [a]
FVC, pre (% predicted)	85.0	21.2
FVC, post (% predicted)	88.2	20.0
FEV_1, pre (% predicted)	81.5	25.0
FEV_1, post (% predicted)	86.6	25.7
D%FEV_1 (%)[a]	*3.2*	*0.8-17.3*
FEV_1/FVC, pre (%)[a]	*83.9*	*78.0-91.6*
FEV_1/FVC, post (%)[a]	*84.4*	*80.8-89.4*
PEF, pre (% predicted)	75.0	25.5
PEF, post (% predicted)	80.7	25.8
FEF_{25-75}, pre (% predicted)	64.4	32.5
FEF_{25-75}, post (% predicted)[a]	*62.6*	*49.7-92.5*

Impulse oscillometry	Mean or *median* [a]	SD or *IQR* [a]
AX (kPa/L)	4.3	2.2
R5-R20 (kPa/(L/s)) [a]	*0.8*	*0.6-0.9*
R5 (kPa/(L/s)) [a]	*1.0*	*0.7-1.3*
R5 (% predicted)	120.9	34.2
R10 (kPa/(L/s)) [a]	*0.7*	*0.5-0.8*
R10 (% predicted)	95.4	22.6
X5 (kPa/(L/s))	-0.5	0.3
X5 (% predicted)	187.4	111.8

[a] Data without normal distribution are expressed as median and interquartile range.

Note: All pulmonary function test parameters are expressed as a percentage of the predicted reference value with “pre” indicating pre-bronchodilator value and “post” indicating post-bronchodilator value.

Abbreviations: SD, standard deviation; IQR, interquartile range; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; D%FEV_1, maximal bronchodilator response (% change in FEV_1); PEF, peak expiratory flow; FEF_{25-75}, forced expiratory flow at 25–75% of the pulmonary volume; AX, reactance area; R, respiratory resistance at certain frequency; X, respiratory reactance at certain frequency

Supplemental Table 2. Correlation of airway parameters measured in segmental bronchi with pre-bronchodilator values of pulmonary function test and post-bronchodilator FEV_1.

		FEV_1/FVC	PEF	FEF_{25-75}	FEV_1, post			FEV_1/FVC	PEF	FEF_{25-75}	FEV_1, post
RUL_WT	ρ	0.138	**-0.463**	-0.240	-0.371	LUL_WT	ρ	0.084	-0.316	-0.251	-0.342
	p-value	0.541	**0.030**	0.282	0.089		p-value	0.711	0.152	0.260	0.119
RUL_WA	ρ	-0.008	**-0.550**	-0.281	**-0.493**	LUL_WA	ρ	0.039	-0.383	-0.293	**-0.439**
	p-value	0.970	**0.008**	0.206	**0.020**		p-value	0.863	0.079	0.186	**0.041**
RUL_LAD	ρ	-0.082	-0.178	-0.076	-0.186	LUL_LAD	ρ	-0.385	-0.047	-0.083	-0.126
	p-value	0.717	0.429	0.738	0.408		p-value	0.077	0.834	0.712	0.577
RUL_LA	ρ	-0.068	-0.169	-0.052	-0.143	LUL_LA	ρ	-0.385	-0.054	-0.082	-0.133
	p-value	0.763	0.453	0.817	0.525		p-value	0.077	0.810	0.715	0.554
RUL_WA/LA	ρ	0.095	-0.052	0.006	0.073	LUL_WA/LA	ρ	0.187	-0.207	-0.097	-0.111
	p-value	0.673	0.820	0.979	0.746		p-value	0.405	0.355	0.667	0.623
RUL_AAD	ρ	-0.113	**-0.471**	-0.232	**-0.424**	LUL_AAD	ρ	-0.089	-0.263	-0.236	-0.341
	p-value	0.617	**0.027**	0.298	**0.049**		p-value	0.695	0.237	0.290	0.121
RUL_AA	ρ	-0.106	**-0.489**	-0.234	**-0.434**	LUL_AA	ρ	-0.072	-0.303	-0.251	-0.381
	p-value	0.640	**0.021**	0.295	**0.044**		p-value	0.751	0.171	0.260	0.080
RML_WT	ρ	0.084	**-0.447**	-0.258	**-0.450**	LLL_WT	ρ	-0.167	-0.320	-0.261	-0.290
	p-value	0.726	**0.048**	0.272	**0.047**		p-value	0.457	0.147	0.240	0.190
RML_WA	ρ	-0.068	**-0.465**	-0.242	**-0.468**	LLL_WA	ρ	-0.197	**-0.433**	-0.341	-0.391
	p-value	0.777	**0.039**	0.304	**0.038**		p-value	0.379	**0.044**	0.120	0.072
RML_LAD	ρ	-0.263	-0.101	0.013	-0.145	LLL_LAD	ρ	-0.283	-0.274	-0.213	-0.277
	p-value	0.262	0.673	0.958	0.542		p-value	0.202	0.217	0.342	0.212
RML_LA	ρ	-0.256	-0.132	0.023	-0.115	LLL_LA	ρ	-0.276	-0.311	-0.262	-0.330
	p-value	0.276	0.578	0.925	0.631		p-value	0.214	0.159	0.239	0.133
RML_WA/LA	ρ	0.156	-0.292	-0.121	-0.135	LLL_WA/LA	ρ	0.156	-0.109	-0.102	-0.055
	p-value	0.510	0.212	0.611	0.572		p-value	0.487	0.630	0.652	0.809
RML_AAD	ρ	-0.078	-0.324	-0.123	-0.354	LLL_AAD	ρ	-0.301	-0.422	-0.339	-0.406
	p-value	0.743	0.163	0.604	0.126		p-value	0.174	0.051	0.122	0.061
RML_AA	ρ	-0.074	-0.342	-0.128	-0.334	LLL_AA	ρ	-0.299	**-0.463**	-0.372	**-0.440**
	p-value	0.758	0.140	0.590	0.151		p-value	0.177	**0.030**	0.088	**0.040**
RLL_WT	ρ	-0.118	**-0.506**	-0.430	-0.409						
	p-value	0.612	**0.019**	0.052	0.066						
RLL_WA	ρ	-0.129	**-0.553**	**-0.463**	**-0.499**						
	p-value	0.579	**0.009**	**0.035**	**0.021**						
RLL_LAD	ρ	-0.095	-0.183	-0.134	-0.284						
	p-value	0.683	0.427	0.562	0.212						
RLL_LA	ρ	-0.126	-0.195	-0.150	-0.279						
	p-value	0.586	0.397	0.516	0.221						
RLL_WA/LA	ρ	-0.026	-0.195	-0.197	0.010						
	p-value	0.911	0.397	0.393	0.966						
RLL_AAD	ρ	-0.264	**-0.489**	-0.400	**-0.480**						
	p-value	0.248	**0.024**	0.072	**0.028**						
RLL_AA	ρ	-0.255	**-0.525**	**-0.436**	**-0.508**						
	p-value	0.264	**0.015**	**0.048**	**0.019**						

Note: Statistically significant values ($p < 0.05$) are marked in bold.

Abbreviations: RUL, right upper lobe; RML right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; WT, wall thickness; WA, wall area; LAD, lumen average diameter; LA, lumen area; AAD, airway average diameter; AA, airway area; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; PEF, peak expiratory flow; FEF_{25-75}, forced expiratory flow at 25–75% of the pulmonary volume

Supplemental Table 3. Quantitative airway parameters measured in subsegmental bronchi and the correlation with pre-bronchodilator FEV_1

	WT			WA			LAD			LA			WA/LA ratio			AAD			AA		
	mm	ρ	p-value	mm^2	ρ	p-value	mm	ρ	p-value	mm^2	ρ	p-value	%	ρ	p-value	mm	ρ	p-value	mm^2	ρ	p-value
Right lung	1.1 ± 0.3	**-0.525**	**0.031**	13.3 ± 4.1	**-0.632**	**0.006**	2.3 ± 0.6	-0.003	0.991	4.9 ± 2.8	-0.020	0.940	393 ± 285.6	-0.332	0.192	4.7 ± 0.6	**-0.491**	**0.045**	18.2 ± 5.2	**-0.512**	**0.036**
RUL	1.2 ± 0.4	-0.465	0.070	14.7 ± 5.7	**-0.532**	**0.034**	2.4 ± 0.6	0.011	0.968	5.1 ± 2.5	0.041	0.881	359.8 ± 198.5	-0.260	0.331	4.8 ± 0.8	-0.435	0.092	19.8 ± 6.4	-0.457	0.075
RML	1 ± 0.2	-0.313	0.276	12 ± 3.7	-0.319	0.266	2.5 ± 0.9	-0.045	0.878	5.6 ± 4.8	-0.014	0.963	303.1 ± 142.3	-0.004	0.989	4.5 ± 0.9	-0.206	0.479	17.6 ± 8	-0.154	0.598
RLL	1.2 ± 0.3	**-0.508**	**0.037**	13.5 ± 4.1	**-0.589**	**0.013**	2.3 ± 0.6	-0.026	0.920	4.7 ± 2.4	-0.062	0.812	432.9 ± 380.3	-0.299	0.244	4.7 ± 0.6	-0.472	0.056	18.2 ± 5.1	**-0.509**	**0.037**
Left lung	1.2 ± 0.3	-0.467	0.059	13.9 ± 5.2	**-0.577**	**0.015**	2.4 ± 0.7	-0.104	0.691	5.1 ± 3	-0.121	0.645	394.5 ± 228.8	-0.213	0.412	4.7 ± 0.8	**-0.487**	**0.048**	19 ± 6.7	**-0.505**	**0.039**
LUL	1.2 ± 0.4	-0.440	0.077	13.1 ± 5.6	-0.440	0.077	2.2 ± 0.7	0.056	0.830	4.3 ± 3.6	0.089	0.735	439 ± 274.8	-0.278	0.280	4.5 ± 0.9	-0.321	0.209	17.4 ± 7.3	-0.295	0.250
LLL	1.2 ± 0.3	-0.451	0.080	15.1 ± 6.2	**-0.597**	**0.015**	2.6 ± 0.8	-0.250	0.349	6.2 ± 3.9	-0.305	0.251	348.6 ± 208.3	-0.074	0.784	5 ± 1	-0.494	0.052	21.4 ± 9	**-0.541**	**0.031**

Note: Statistically significant values ($p < 0.05$) are marked in bold.

Abbreviations: RUL, right upper lobe; RML right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; WT, wall thickness; WA, wall area; LAD, lumen average diameter; LA, lumen area; AAD, airway average diameter; AA, airway area

Supplemental Table 4. Correlation of emphysema parameters with pre-bronchodilator values of pulmonary function test and post-bronchodilator FEV_1

		FEV_1/FVC		PEF		FEF_{25-75}		FEV_1, post[a]		R5		R10		X5		AX	
		ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value
Right lung	EV	-0.229	0.294	-0.369	0.083	-0.376	0.077	**-0.474**	**0.022**	0.114	0.605	0.000	1.000	**0.643**	**0.001**	-0.007	0.975
	ER	-0.164	0.454	-0.259	0.232	-0.118	0.592	-0.255	0.240	0.204	0.349	0.131	0.553	0.230	0.292	0.339	0.114
RUL	EV	-0.243	0.263	-0.379	0.074	-0.399	0.059	**-0.490**	**0.018**	0.131	0.551	-0.004	0.986	**0.693**	**0.000**	0.001	0.998
	ER	-0.232	0.286	-0.266	0.220	-0.180	0.411	-0.342	0.110	0.296	0.170	0.207	0.344	**0.441**	**0.035**	0.406	0.054
RML	EV	-0.113	0.606	-0.224	0.305	-0.212	0.331	-0.328	0.127	0.016	0.943	0.090	0.684	0.338	0.114	-0.144	0.511
	ER	0.097	0.660	0.004	0.985	0.176	0.421	0.109	0.621	0.129	0.559	0.117	0.594	-0.199	0.363	0.338	0.115
RLL	EV	-0.234	0.282	-0.378	0.075	-0.381	0.073	**-0.475**	**0.022**	0.119	0.589	-0.018	0.935	**0.648**	**0.001**	0.020	0.929
	ER	-0.193	0.379	-0.333	0.120	-0.190	0.385	-0.299	0.166	0.187	0.393	0.081	0.713	0.264	0.224	0.300	0.165
Left lung	EV	-0.319	0.138	-0.410	0.052	**-0.481**	**0.020**	**-0.571**	**0.004**	0.172	0.433	0.072	0.743	**0.712**	**0.000**	0.027	0.901
	ER	-0.379	0.075	-0.169	0.440	-0.311	0.149	**-0.450**	**0.031**	0.311	0.148	0.345	0.107	0.279	0.197	**0.446**	**0.033**
LUL	EV	-0.209	0.339	-0.296	0.170	-0.365	0.087	**-0.461**	**0.027**	0.091	0.679	0.020	0.927	**0.644**	**0.001**	-0.070	0.752
	ER	-0.126	0.567	0.127	0.565	0.021	0.926	-0.152	0.489	0.198	0.365	0.283	0.191	0.121	0.583	0.360	0.091
LLL	EV	-0.376	0.077	**-0.465**	**0.026**	**-0.535**	**0.009**	**-0.617**	**0.002**	0.217	0.320	0.103	0.639	**0.723**	**0.000**	0.090	0.683
	ER	-0.408	0.053	-0.255	0.240	**-0.420**	**0.046**	**-0.517**	**0.011**	0.261	0.230	0.237	0.276	0.325	0.130	0.383	0.071

[a] Post-bronchodilator FEV_1

Note: Statistically significant values ($p < 0.05$) are marked in bold.

Abbreviations: RUL, right upper lobe; RML right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; EV, emphysema volume; ER, emphysema ratio; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; PEF, peak expiratory flow; FEF_{25-75}, forced expiratory flow at 25–75% of the pulmonary volume; AX, reactance area; R, respiratory resistance at certain frequency; X, respiratory reactance at certain frequency

ABSTRACT(IN KOREAN)

소아 감염 후 폐쇄성 세기관지염 환자에서 컴퓨터 단층촬영의 정량적 분석과 폐 기능과의 상관관계

<지도교수 이미정>

연세대학교 대학원 의학과

김종현

목적: 소아 감염 후 폐쇄성 세기관지염 (PIBO) 환자에서 컴퓨터 단층촬영 (CT)을 기반으로 한 정량적 기도 및 폐기종 부피 측정의 유용성과 폐 기능과의 상관관계 조사.

재료 및 방법: 후향적 연구로서, PIBO로 진단된 소아 환자의 흉부 CT와 폐 기능 검사 (PFT) 결과를 이용하였다. 흉부 CT에서 분절 기관지와 아분절 기관지에 대한 정량적 분석을 시행하였다. 폐기종 용적은 정상 폐와 공기 가둠 현상이 있는 부위의 폐에서 각각 측정한 CT 감쇠 값의 평균보다 낮은 감쇠 값을 가지는 부분의 용적으로 정의하였으며 폐의 각 엽에서 측정하였다. 전체 폐 용적 대비 폐기종 용적의 비도 계산하였다. PFT에서는 폐활량 검사 변수들과 임펄스 오실로미터법 변수들을 측정하였다. 피어슨 또는 스피어만 상관분석을 통해 CT에서 측정한 변수와 PFT 결과 사이의 상관관계를 조사하였다.

결과: 총 23명의 환자가 포함되었으며, 연령은 4세에서 15세 사이, 평균 7.0 ± 3.3 세였다. 총 371(371/414, 89.6%)개의 분절

기관지와 242(242/414, 58.5%)개의 아분절 기관지에서 정량적 분석이 성공적으로 이루어졌다. 기도 분석에서, 기도 벽의 면적은 대부분의 엽에서 1초 강제 호기량 (FEV_1)과 음의 상관관계를 보였다. 양측 하엽에서는 평균 기도 지름과 기도 면적이 FEV_1과 음의 상관관계를 보였다. 폐기종 분석에서는 폐기종 용적이 FEV_1과 음의 상관관계를 보였고, 오실로미터법 변수 중 5Hz에서의 리액턴스와 양의 상관관계를 보였다.

결론: 흉부 CT를 이용한 기도와 폐기종의 정량적 측정은 PIBO 환아에서 폐 기능을 보여줄 수 있다.

핵심되는 말: 폐, 컴퓨터 단층촬영, 폐 기능 검사, 폐쇄성 세기관지염, 소아, 정량적 영상