Assessment of proximal and peripheral airway dysfunction by computed tomography and respiratory impedance in asthma and COPD patients with fixed airflow obstruction

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Abstract:

OBJECTIVE: To ascertain: (i) if elderly patients with fixed airflow obstruction (FAO) due to asthma and chronic obstructive pulmonary disease (COPD) have distinct airway morphologic and physiologic changes; (ii) the correlation between the morphology of proximal/peripheral airways and respiratory impedance.

METHODS: Twenty-five asthma cases with FAO and 22 COPD patients were enrolled. High-resolution computed tomography was used to measure the wall area (WA) and lumen area (LA) of the proximal airway at the apical segmental bronchus of the right upper lobe (RB1) adjusted by body surface area (BSA) and bronchial wall thickening (BWT_r) of the peripheral airways and extent of expiratory air trapping (AT_{exp}). Respiratory impedance included resistance at 5 Hz (R_5) and 20 Hz (R_{20}) and resonant frequency (Fres). Total lung capacity (TLC) and residual volume (RV) were measured.

RESULTS: Asthma patients had smaller RB1-LA/BSA than COPD patients (10.5 ± 3.4 *vs.* 13.3 ± 5.0 mm^2/m^2, $P = 0.037$). R_5 (5.5 ± 2.0 *vs.* 3.4 ± 1.0 $cmH_2O/L/s$, $P = 0.02$) and R_{20} (4.2 ± 1.7 *vs.* 2.6 ± 0.7 $cmH_2O/L/s$, $P = 0.001$) were higher in asthma cases. AT_{exp} and BWT_r were similar in both groups. Regression analysis in asthma showed that forced expiratory volume in one second (FEV_1) and Fres were associated with RB1-WA/BSA ($R^2 = 0.34$, $P = 0.005$) and BWT_r (0.5, 0.012), whereas RV/TLC was associated with AT_{exp} (0.38, 0.001).

CONCLUSIONS: Asthma patients with FAO had a smaller LA and higher resistance of the proximal airways than COPD patients. FEV_1 and respiratory impedance correlated with airway morphology.

Keywords:

Airway wall thickness, airway lumen area, expiratory air trapping, impulse oscillometry, respiratory impedance

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People suffering from asthma with airway remodeling may have a fixed airflow obstruction (FAO) phenotype similar to that in patients with chronic obstructive pulmonary disease (COPD),[1] but the mechanisms of FAO in both entities are quite different. In asthma, structural changes in the proximal and small airways

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are attributed primarily to increased smooth muscle mass, hyperplasia of submucosal glands, and/or eosinophilic infiltration.[2,3] Unlike asthma, structural changes in COPD usually involve small airways and are largely attributed to fibrosis in the airway wall, which result in reduction of elastic recoil and/or airway luminal narrowing.[4]

A study comparing COPD patients with age-matched older asthma patients with a similar degree of airflow limitation found that the latter had lower residual volume (RV), higher diffusing capacity, and lower emphysema score on high-resolution computed tomography (HRCT).[5] With regard to airway dimensions and air trapping, one study showed no differences between young asthma patients and COPD patients.[6] In contrast, another study showed greater wall thickness of third-to-sixth-generation bronchi on HRCT in age-matched older asthma patients than in COPD patients.[7]

Peripheral airway dysfunction (PAD) can be assessed at the physiologic level by measurement of RV and the ratio of RV to total lung capacity (RV/TLC) to determine air trapping as a result of the early closure of peripheral airways. It can also be assessed by impulse oscillometry (IOS) to detect alterations in respiratory impedance (i.e., peripheral airway resistance and the reactance of the respiratory system). Several studies have shown a direct relationship between increased RV and increased peripheral airway resistance in asthma[8-11] and COPD.[12] Recent studies have demonstrated that IOS parameters (i.e., the difference between resistance at low frequency (5 Hz, R_5) and high frequency (20 Hz, R_{20}) [R_5–R_{20}] and resonant frequency [Fres]) can be used to identify PAD in patients with asthma[13] as well as a reduction in reactance at 5 Hz (X5) along with an increase in Fres as physiologic markers of PAD in COPD patients.[14]

We aimed to ascertain: (i) if patients with FAO from asthma and COPD have different morphologic HRCT findings and respiratory impedance; (ii) the correlations of morphologic changes of proximal and peripheral airways with physiologic parameters.

Methods

This was a prospective cross-sectional study approved by the Ethics Review Board of Ramathibodi Hospital (Mahidol University, Bangkok, Thailand). Written informed consent was obtained from all participants.

We enrolled consecutive asthma and COPD patients aged ≥60 years who had FAO. The latter was defined as forced expiratory volume in one second (FEV_1)/forced vital capacity <0.7 and FEV_1 ≤80% predicted (after inhalation of 400 μg of salbutamol).[15] Asthma cases were those with physician-diagnosed asthma based on the Global Initiative for Asthma guidelines 2012,[16] never-smoked status, or nonsignificant smoking history of <10 pack-years and a history of childhood asthma or previously documented variable airflow obstruction to inhaled salbutamol. COPD patients fulfilled the diagnostic criteria of the Global Initiative for Chronic Obstructive Lung Disease guidelines 2013,[15] including a smoking history of ≥10 pack-years. Patients with a history of exacerbation within 8 weeks before entering the study or a history of previous thoracic surgery were excluded from the study.

Demographic data, disease duration, smoking history, symptom score (asthma control test [ACT, range 5–25], modified Medical Research Council dyspnea scale [mMRC, range 0–4], COPD assessment test [CAT, range 0–40]), and medications were recorded.

Computed tomography protocol

HRCT was undertaken on a multidetector-row computed tomography (CT) scanner (Sensation Cardiac 64; Siemens Healthcare, Erlangen, Germany) or Brilliance iCT SP (Philips, Best, The Netherlands). Inspiratory and expiratory HRCT images were acquired using volumetric acquisition in the craniocaudal direction. CT parameters were 64 detectors ×0.5-mm collimation, a gantry rotation time of 0.33 s, and a pitch of 0.9-1.45 depending on the machine used. Before CT, each patient was taught the technique for deep inspiration and breath-hold and how to carry out dynamic forced expiration throughout the scan. End-inspiratory CT images were obtained first using the tube potential of 120 kVp and the tube current-time product of 70–180 mAs. Dynamic forced expiratory CT was done subsequently and coordinated with the onset of the expiratory effort using the tube potential of 100 kVp or 120 kVp and the tube current-time product of 40–100 mAs. Images were retro-reconstructed with a section thickness of 1 mm and section interval of 0.7 mm and with low-and high-spatial-frequency algorithms for mediastinal window (window level, 40 HU; window width, 400 HU) and lung window (window level, −650 HU; window width, 1450 HU) displays, respectively.

Two thoracic radiologists, who were blinded to the diagnosis and clinical data, reviewed HRCT images independently.

Assessment of the morphology of the proximal airways

The morphology of the proximal airways was measured at the apical segmental bronchus of the right upper lobe (RB1) using an electronic outlining tool at the level where its external perimeter was clearly visible.[17] Briefly, the external perimeter and the area within the internal perimeter at inspiration of RB1 were considered to be the total area (RB1-TA) and lumen area (RB1-LA), respectively [Supplement 1a and b]. The wall area (RB1-WA) was calculated subsequently by subtracting RB1-LA from RB1-TA. The percentage of RB1-WA (%RB1-WA) was calculated using the formula: 100× (RB1 - WA/RB1 - TA). RB1-TA, RB1-LA, and RB1-WA were then normalized by body surface area (BSA) based on the Du Bois formula.

Assessment of the morphology of the peripheral airways

HRCT images were obtained and magnified (×5-fold) for measurement of bronchial-wall thickness (BWT) at six anatomic zones of each lung [Supplement 2a]: zone 1, between the apex and the crossing left brachiocephalic vein; zone 2, below zone 1 to the mid-aortic arch; zone 3, below zone 2 to the carina; zone 4, below zone 3 to 1 cm below the origin of the right bronchus intermedius; zone 5, below zone 4 to the right inferior pulmonary vein; zone 6, below zone 5 to 1 cm below the right hemidiaphragm dome.[17]

By assuming that BWT was constant on a cross-sectional image, we determined BWT by subtracting the internal diameter of the bronchus from its external diameter (ED) and dividing the remainder by two. The measurement was chosen at the most clearly visible and thickest fourth-generation (subsegmental), fifth-generation (sub-subsegmental) or sixth-generation (sub-sub-subsegmental) bronchi lying perpendicular to or obliquely or transversely on a magnified axial image [Supplement 2b].[18] The relative BWT (BWT_r) was then calculated (BWT/ED). BWT_r was graded on a four-point scale: Grade 0, <0.2; Grade 1, 0.2 to <0.4; Grade 2, 0.4 to <0.8; Grade 3, ≥0.8.

Assessment of expiratory air trapping

Visual assessment of AT_{exp} was carried out using a method adapted from a study by Suwatanapongched *et al*.[17] The dynamic forced expiratory and end-inspiratory HRCT images in each examination were compared for the evaluation of air trapping. AT_{exp} was considered to be present if a lung region exhibited a less than normal increase in attenuation or no change in volume during expiration as compared with the corresponding lung region on paired end-inspiratory CT images. The extent of AT_{exp} was graded on a five-point scale: Grade 0, no visible AT_{exp}; Grade 1, 1%–25%; Grade 2, 26%–50%; Grade 3, 51%–75%; and Grade 4, 76%–100% of the cross-sectional area of each lung zone [Supplement 3].

Assessment of emphysema

Emphysema was considered if there were focal areas of low attenuation (less than − 950 HU on inspiratory HRCT images). The extent of emphysema was graded on a five-point scale: Grade 0, no visible emphysema; Grade 1, 1%–25%; Grade 2, 26%–50%; Grade 3, 51%–75%; and Grade 4, 76%–100% of the cross-sectional area of each lung zone.

The BWT_r, AT_{exp}, and emphysema scores from each zone were summed; the possible scores were 0–36, 0–48, and 0–48, respectively.

Pulmonary function tests

All pulmonary function tests were conducted within 1 month before or after HRCT examination. Spirometry, single-breath diffusing capacity of the lungs for carbon monoxide transfer coefficient (*K*CO), airway resistance (Raw), TLC, and RV were measured with a plethysmograph (Cardinal Health, Yorba Linda, CA, USA) with respect to standard recommendations.[19,20] Severe airflow obstruction was considered if the postbronchodilator FEV_1 was ≤60% predicted in asthma[21] and <50% predicted in COPD.[15] Significant air trapping was considered if the RV/TLC ratio was >40%.[22]

Respiratory impedance was assessed by IOS using a Master Screen™ Impulse Oscillometry (Erich Jaeger, Friedberg, Germany).[23] We measured R_5 and R_{20}, which reflect the total and proximal airway resistance, respectively. The difference between R_5 and R_{20} (R_5–R_{20}), which reflects peripheral airway resistance, was subsequently calculated. Reactance at 5 Hz (X_5) and reactance area (AX), which are markers of changes in pulmonary compliance caused by airflow obstruction, were measured. Fres (the frequency at which the reactance of the respiratory system is zero and at which the total impedance to airflow is entirely flow resistive) was measured. A reduction in X_5 and increases in AX area or Fres designate PAD.[24]

Statistical analyses

Continuous variables are the mean and standard deviation. The unpaired *t*-test and Mann–Whitney U-test were used for comparisons between groups, as appropriate. Chi-square or Fisher's exact tests were used for comparison of categorical variables between groups. For assessment of the correlations between physiologic parameters and HRCT parameters (RB1 morphology, BWT_r, AT_{exp}, and emphysema scores), Pearson correlation or Spearman rank correlation were applied for normal and nonnormal data, as appropriate. A multiple linear regression model with stepwise selection for predicting HRCT parameters was applied further to test variables that were significant on the univariate analysis. To avoid multicollinearity as much as possible, if the correlation coefficient between independent variables was >0.4, each variable was used separately as an independent variable in the model.

The interobserver agreement between the two readers on HRCT scoring for continuous measures was tested using Lin's concordance correlation coefficient (Pearson's ρ). $\rho < 0.90$ was considered to indicate poor agreement; 0.90–0.95, moderate agreement; 0.95–0.99, substantial agreement; and >0.9, almost perfect agreement.[25] Statistical analyses were done using SPSS v17.0 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered significant.

Results

The clinical characteristics and physiologic parameters of the 25 asthma patients and 22 COPD patients are summarized in Table 1. The ACT score in asthma was 21.2 ± 3.4, whereas the mMRC and CAT scores in COPD were 1.32 ± 0.6 and 12.6 ± 6.8, respectively.

High-resolution computed tomography parameters of right upper lobe morphology, bronchial wall thickening, expiratory air trapping, and emphysema

Interobserver agreement showed substantial concordance with the values of Pearson's ρ: 0.98 for RB1-LA and RB1-WA, 0.95 for AT_{exp}, 0.98 for emphysema, and 0.8 for BWT_r. The final scoring decision was reached by consensus between the two readers.

RB1 morphology, BWT_r, AT_{exp}, and emphysema are shown in Table 2. RB1-LA and RB1-LA/BSA were significantly smaller in asthma patients than in COPD patients ($P = 0.014$ and $P = 0.037$, respectively). In contrast, BWT_r and AT_{exp} scores were not different between the two groups. Three of 25 asthma cases showed a small extent of emphysema with scores of 6, 8, and 9, all of whom had normal *K*CO.

When categorized by FEV_1, asthma patients who had $FEV_1 \leq 60\%$ predicted had a higher BWT_r score than those who had $FEV_1 \geq 60\%$ predicted [Figure 1a]. There were no differences in AT_{exp}, RB1-LA/BSA, or RB1-WA/BSA between the two asthma subgroups [Figure 1b, e and h]. When categorized by air trapping, asthma patients who had a RV/TLC ratio >40% showed a higher AT_{exp} score than those who had a RV/TLC ratio ≤40% and showed a higher AT_{exp} score than COPD patients who had a RV/TLC ratio >40% [Figure 1d]. There were no significant differences in BWT_r or AT_{exp} scores or RB1 morphology between COPD subgroups categorized by FEV_1 [Figure 1a, b, e and f] or the RV/TLC ratio [Figure 1c, d, g and h].

Impulse oscillometry parameters

IOS parameters are shown in Table 3. Although peripheral airway resistance (R_5–R_{20}) was not significantly different, R_5 and R_{20} were significantly greater in asthma cases than in COPD patients ($P = 0.022$ and $P = 0.001$, respectively). In addition, a significant reduction in X_5 ($P = 0.027$) with a nonsignificant trend of increasing AX ($P = 0.073$) was observed toward asthma patients rather than COPD patients.

Table 1: Clinical characteristics and baseline physiologic parameters of elderly asthma patients with fixed airflow obstruction and chronic obstructive pulmonary disease patients

Clinical characteristics and pulmonary function parameters	Asthma with FAO (*n*=25)	COPD (*n*=22)	*P*
Male, *n* (%)	4 (16)	21 (84)	<0.001
Age (years)	69±6	73±7	0.031
Duration of being diagnosed, years*	14 (2, 60)	2 (1, 11)	<0.001
Smoking, pack-years*	0 (0, 5)	17 (10, 120)	<0.001
Body mass index, kg/m^2	24.5±4.0	22.6±4.3	0.13
Asthma control, *n* (%)			
Well controlled	5 (7.1)		
Partially controlled	15 (21.4)		
Poorly controlled	5 (7.1)		
Treatment, *n* (%)			
ICS	25 (100)	16 (72)	0.005
ICS/LABA	24 (96)	14 (63)	0.005
Montelukast	14 (56)	1 (4.5)	<0.001
LAMA	5 (20)	18 (82)	<0.001
Pre-BD FEV_1, % predicted	63.3±11.5	62.4±19.1	0.841
Pre-BD FVC, % predicted	88.3±14.8	86.8±13.4	0.711
Pre-BD FEV_1/FVC	0.60±0.11	0.51±0.11	0.006
Pre-BD $FEF_{25-75\%}$, % predicted	30.9±18.4	24.9±14.3	0.228
Post-BD FEV_1, % predicted	67.0±10.3	65.9±18.9	0.797
Post-BD FVC, % predicted	90.6±15.0	88.3±13.2	0.585
Post-BD FEV_1/FVC	0.62±0.1	0.53±0.1	0.006
Post-BD $FEF_{25-75\%}$, % predicted	34.8±19.0	28.2±14.9	0.199
TLC, % predicted	92.7±13.6	96.9±12.4	0.274
RV, % predicted	101.9±24.1	95.2±25.6	0.361
RV/TLC, %	43.8±5.8	41.8±8.0	0.312
DLCO, % predicted	79.0±16.4	78.7±23.1	0.962
*K*CO, % predicted	109.4±22.2	82.3±21.3	<0.001

*Data are the median (range), Data are the mean±SD. Pre-BD = Pre-bronchodilator values, Post-BD = Post-bronchodilator values, ICS = Inhaled corticosteroid, LABA = Long-acting β2-agonist, LAMA = Long-acting antimuscarinic agent, FEV_1 = Forced expiratory volume in 1 s, FVC = Forced vital capacity; $FEF_{25\%-75\%}$ = Forced expiratory flow rate between 25% and 75% of vital capacity, TLC = Total lung capacity, RV = Residual volume, DLCO = Diffusing capacity of the lungs for carbon monoxide, KCO = Carbon monoxide transfer coefficient, FAO = Fixed airflow obstruction, COPD = Chronic obstructive pulmonary disease

Correlations between pulmonary function tests and right upper lobe morphology, bronchial wall thickening, and expiratory air trapping

There was an inverse correlation between RB1-WA/BSA and FEV_1 (%predicted) in asthma cases ($r = -0.4$, $P = 0.035$) and COPD patients ($r = -0.6$, $P = 0.015$). In asthma cases, RB1-WA/BSA was correlated with the RV/TLC ratio ($r = 0.4$, $P = 0.04$), and RB1-LA/BSA was correlated with airway resistance (Raw) ($r = 0.4$, $P = 0.05$). Similar findings were not observed in COPD patients.

Table 2: High-resolution computed tomography right upper lobe apical segmental bronchus morphologic parameters and relative bronchial-wall thickness score and expiratory air trapping score of elderly asthma patients with fixed airflow obstruction and chronic obstructive pulmonary disease patients

HRCT scores	Asthma with FAO (*n*=25)	COPD (*n*=22)	*P*
RB1-LA, mm^2	16.7±5.1	21.8±7.7	0.014
RB1-LA/BSA, mm^2/m^2	10.5±3.4	13.3±5.0	0.037
RB1-TA, mm^2	38.8±9.3	47.7±14.9	0.034
RB1-TA/BSA, mm^2/m^2	24.2±5.8	29.0±9.6	0.074
RB1-WA, mm^2	22.1±5.2	25.9±8.1	0.086
RB1-WA/BSA, mm^2/m^2	13.7±2.9	15.7±4.9	0.147
%RB1-WA	57.6±7.1	54.6±4.4	0.127
BWT_r	11.0±1.7	10.8±1.4	0.563
Mean BWT_r	0.27±0.04	0.267±0.02	0.735
AT_{exp}	33.4±11.3	29.4±10.7	0.221
Emphysema*	0 (0, 9)	9 (1, 46)	<0.001

*Data are the median (range), Data are the mean±SD. RB1 = Right upper lobe apical segmental bronchus; RB1-LA = Lumen area, RB1-TA = Total area, %RB1-WA = Wall area, BSA = Body surface area, AT_{exp} = Air trapping score on expiratory scan, BWT_r = Relative bronchial-wall thickness score, mean BWT_r = Average value of the relative bronchial-wall thickness values from 12 lung zones, HRCT = High-resolution computed tomography, FAO = Fixed airflow obstruction, COPD = Chronic obstructive pulmonary disease

Table 3: Impulse oscillometry parameters and airway resistance of elderly asthma patients with fixed airflow obstruction and chronic obstructive pulmonary disease patients

IOS index	Asthma with FAO (*n*=25)	COPD (*n*=22)	*P*
R5, $cmH_2O/L/s$	5.5±2.0	4.2±1.7	0.022
R20, $cmH_2O/L/s$	3.4±1.0	2.6±0.7	0.001
R5 - R20, $cmH_2O/L/s$*	1.76 (0.8, 5.2)	1.23 (0.3, 4.5)	0.138
R5 - R20/R5, %	35.1±9.9	34.9±12.1	0.955
X5, $cmH_2O/L/s$*	−2.4 (−8.4, −1.7)	−1.7 (−5.0, −0.8)	0.027
AX, cmH_2O/L*	20.6 (7.1, 75.8)	11.5 (1.6, 44.9)	0.073
Fres, Hz	23.4±5.6	22.1±6.6	0.466
Raw, $cmH_2O/L/s$	3.0±1.3	2.4±1.3	0.113
Raw, % predicted	191.5 (83.9)	163.0 (83.0)	0.250

*Data are the median (range), All IOS parameters are pre-bronchodilator values, Data are the mean±SD. R_5 = Resistance at 5 Hz, R_{20} = Resistance at 20 Hz, X_5 = Reactance at 5 Hz, AX = Reactance area, Fres = Resonant frequency, R_{aw} = Airway resistance (plethysmography), IOS = Impulse oscillometry, FAO = Fixed airflow obstruction, COPD = Chronic obstructive pulmonary disease

In asthma patients, there was an inverse correlation between the BWT_r score and FEV_1 (%predicted) ($r = -0.6$, $P < 0.001$). The BWT_r score was correlated with airway resistance (plethysmography) ($r = 0.5$, $P = 0.005$) and the RV/TLC ratio ($r = 0.5$, $P = 0.008$), whereas the AT_{exp} score was correlated with the RV/TLC ratio ($r = 0.6$, $P < 0.001$) [Table 4].

In COPD, the BWT_r score was inversely correlated with FEV_1%predicted ($r = -0.47$, $P = 0.013$). Emphysema score was correlated with TLC %predicted ($r = 0.6$, $P = 0.003$)

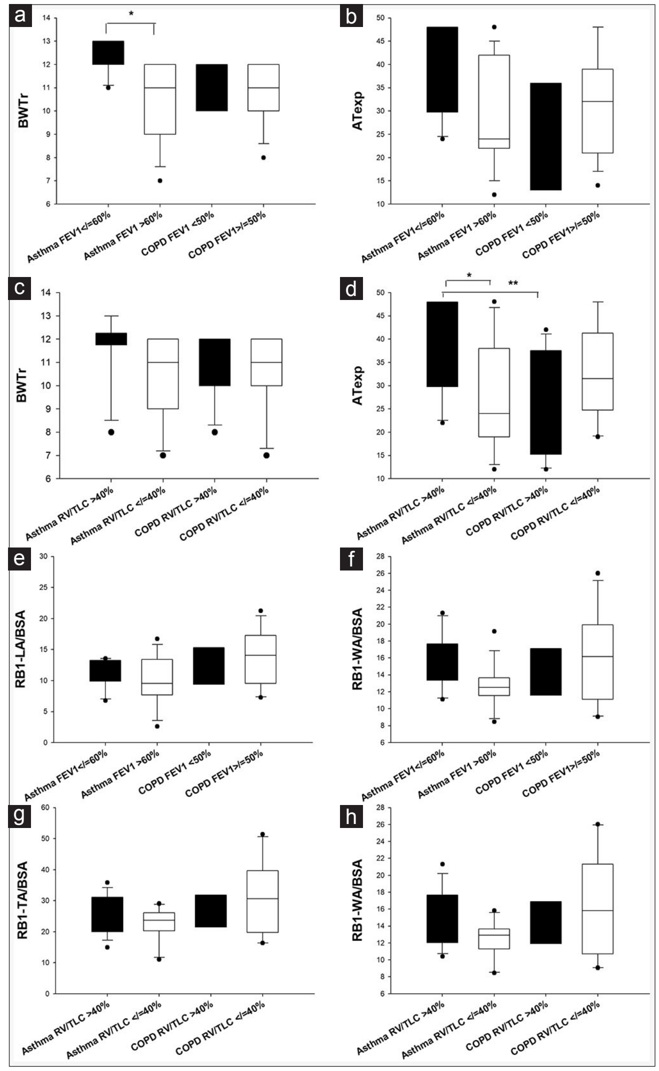

Figure 1: Box plot showing the bronchial wall thickening and expiratory air trapping score in asthma and chronic obstructive pulmonary disease categorized by severity assessed by forced expiratory volume in one second (a and b) and residual volume/total lung capacity ratio (c and d). The right upper lobe-lumen area/body surface area, right upper lobe-wall area/body surface area, and right upper lobe-total area/body surface area in both groups plotted in forced expiratory volume in one second and residual volume/total lung capacity categorization are shown in (e-h). *$P < 0.05$ asthma with forced expiratory volume in one second of ≤60% predicted versus asthma with forced expiratory volume in one second of >60% predicted, and asthma with a residual volume/total lung capacity ratio of >40% versus asthma with a residual volume/total lung capacity ratio of ≤40. **$P < 0.05$ asthma with a residual volume/total lung capacity ratio of >40% versus chronic obstructive pulmonary disease with a residual volume/total lung capacity ratio of >40%

and inversely correlated with *KCO* ($r = -0.6$, $P = 0.004$). IOS parameters were correlated significantly with the AT_{exp} score [Table 4].

Multiple linear regression analysis using the parameters, i.e., FEV_1, TLC, *KCO* (%predicted), RV/TLC, and Fres to predict RB1-WA/BSA, RB1-LA/BSA, and scores of BWT_r, AT_{exp}, and emphysema is shown in Table 5. In asthma patients, FEV_1 (%predicted) together with Fres was independently associated with the

Table 4: Correlation between high-resolution computed tomography parameters and impulse oscillometry parameters in elderly asthma patients with fixed airflow obstruction and chronic obstructive pulmonary disease patients

Group	HRCT parameter	R_5	R_{20}	R_5 - R_{20}	X_5	AX	Fres
Asthma with FAO	RB1-LA/BSA	−0.44 (0.030)	−0.13 (0.530)	−0.40 (0.013)*	0.44 (0.030)*	−0.45 (0.023)*	0.42 (0.040)
	BWT_r	0.40 (0.040)	−0.24 (0.2)	0.50 (0.012)*	−0.35 (0.080)*	0.44 (0.032)*	0.60 (0.001)
	AT_{exp}	0.31 (0.130)	0.05 (0.816)	0.51 (0.009)*	−0.39 (0.050)*	0.46 (0.020)*	0.50 (0.007)
COPD	AT_{exp}	−0.53 (0.011)	−0.36 (0.10)	−0.54 (0.01)*	0.44 (0.040)*	−0.47 (0.029)*	−0.50 (0.008)

*Data are expressed as the Spearman rank correlation coefficient and *P* value (parentheses), Data are expressed as the Pearson correlation coefficient and *P* value (parentheses), R_5 = Resistance at 5 Hz, R_{20} = Resistance at 20 Hz, X_5 = Reactance at 5 Hz, AX = Reactance area, Fres = Resonant frequency, RB1-LA/BSA = Lumen area of the right upper lobe apical segmental bronchus adjusted by body surface area; BWT_r = Relative bronchial wall thickness score; AT_{exp} = Air trapping score on expiratory scan, FAO = Fixed airflow obstruction, COPD = Chronic obstructive pulmonary disease, , HRCT = High-resolution computed tomography

Table 5: Multiple linear regression models for prediction of right upper lobe apical segmental bronchus wall area adjusted by body surface area, relative bronchial-wall thickness score, air trapping score on expiratory scan, and emphysema scores in elderly asthma patients with fixed airflow obstruction and chronic obstructive pulmonary disease patients

Groups	HRCT parameter	Physiologic parameter	β	*P*	R^2	95% CI for β	
						Lower	Upper
Asthma with FAO	RB1-WA/BSA	FEV_1(%predicted)	−0.16	0.005	0.34	−0.26	−0.05
		Fres	−0.23	0.04		−0.44	−0.09
	BWT_r	FEV_1 (%predicted)	−0.07	0.012	0.50	−0.12	−0.02
		Fres	0.11	0.036		0.01	0.22
	AT_{exp}	RV/TLC (%)	1.20	0.001	0.38	0.50	1.90
COPD	RB1-WA/BSA	FEV_1(%predicted)	0.13	0.024	0.30	0.02	0.25
	BWT_r	FEV_1 (%predicted)	−0.03	0.026	0.22	−0.06	−0.005
	AT_{exp}	Fres	−0.80	0.016	0.26	−1.50	−0.20
	Emphysema	TLC (%predicted)	0.54	0.014	0.70	0.12	0.95
		*K*CO (%predicted)	−9.60	0.017		−17.30	−1.90

 = Unstandardized coefficient, 95% CI: 95% confidence interval, RB1-WA/BSA = Wall area of the right upper lobe apical segmental bronchus adjusted by body surface area; BWT_r = Relative bronchial wall thickness score, AT_{exp} = Air trapping score on expiratory scan, FEV_1 = Forced expiratory volume in one second , Fres = Resonant frequency, RV/TLC = Ratio of residual volume to total lung capacity, TLC = Total lung capacity, KCO = Carbon monoxide transfer coefficient, FAO = Fixed airflow obstruction, COPD = Chronic obstructive pulmonary disease, HRCT = High-resolution computed tomography

RB1-WA/BSA and BWT_r score with R^2 of 0.34 and 0.50, respectively. RV/TLC was independently associated with the AT_{exp} score with R^2 of 0.38 ($P = 0.001$). In COPD, FEV_1 (%predicted) was independently associated with RB1-WA/BSA (R^2 = 0.30, P = 0.024) and BWT_r score (R^2 = 0.22, P = 0.026); Fres was independently associated with the AT_{exp} score ($R^2 = 0.26$, $P = 0.016$); TLC together with *K*CO were independently associated with the emphysema score ($R^2 = 0.7$, $P = 0.001$).

Discussion

The present study showed that the morphologic changes of the smaller RB1 LA and higher resistance in proximal airways as assessed by IOS were more obvious in patients with FAO due to asthma than COPD. In contrast, the BWT_r score and AT_{exp} score, as well as the resistance and reactance in the peripheral airways of elderly asthma cases, were on a par with those of COPD patients.

HRCT studies in asthma have shown increased thickening of airway walls to be associated with smoking, a longstanding course of asthma, or severe asthma.[26,27] An increase in the RB1 WA[27] and the wall thickness of peripheral airways as well as air trapping are associated with reduced FEV_1.[28] Those findings are consistent with data from our study. We found respiratory impedance (R_5 and R_5–R_{20}) and reactance to be correlated with RB1-LA/BSA and BWT_r. In addition to FEV_1, Fres was another independent determinant of RB1-WA/BSA and BWT_r.

Despite consistency with studies showing a higher BWT_r score in asthma cases with FEV_1 <60% predicted than those with FEV_1 ≥60% predicted,[26,27] no such difference was found in the morphology of proximal airways (RB1) in our study. This could be a result of the effect of treatment with inhaled corticosteroids (affecting mainly the proximal airways, with limited effectiveness in the peripheral airways).[29] In contrast to a study by Kosciuch *et al.*,[30] because our asthma patients had a smoking history of <5 pack-years, increased BWT_r was likely attributed to disease severity and the longstanding course of the disease. The AT_{exp} score was correlated closely with the RV/TLC ratio, a finding that is consistent with studies on air trapping in young and old asthma cases.[6] There was no significant difference in increased air trapping between asthma and COPD groups, particularly among those who had FEV_1 between 50% predicted and 80% predicted. This finding was in contrast to a study by Hartley *et al.* using lung density on quantitative CT as a marker of air trapping. They demonstrated that air trapping increased in asthma patients to a lesser extent than in patients with COPD.[31] That study included patients who were younger and with less severe asthma compared with our study. However, when grouping by the RV/TLC ratio, asthma patients with a higher RV/TLC ratio showed a greater AT_{exp} score on HRCT than those with a lower RV/TLC ratio and those with COPD, suggesting that the RV/TLC ratio is superior to FEV_1 in depicting air trapping on HRCT.

In COPD, FEV_1 was the only determinant for RB1-WA/BSA and BWT_r in the regression model. There was poor correlation between the AT_{exp} score and physiologic parameters of air trapping. The possible explanation was a limitation of our technique to distinguish air trapping in emphysematous areas. Further study on the peripheral airways in COPD with more advanced CT technology is required.

Interestingly, increase in RB1-WA and smaller LA in the asthma group suggested remodeling of the proximal airways, and this was a stark difference from the COPD group. This observation is consistent with that from other reports.[7,31] The IOS parameter of a greater increase in proximal airway resistance (R_{20}) was also observed in asthma patients than in COPD patients without the influence of body size on measurable RB1 morphology in the present study. This phenomenon may be explained by episodic bronchoconstriction of the proximal airways by methacholine provocation, which can cause ongoing airway remodeling.[32] In addition, bronchoconstriction could be associated with intraluminal mucosal folding. This would result in increased amounts of luminal fluid leaking from the airway wall and further enhancing bronchoconstriction to cause proximal airway resistance.[33]

The present study had four main limitations. First, the methacholine test was not carried out for the diagnosis of asthma because a low FEV_1 would have exposed participants to airway obstruction. However, asthma patients showed at least one previously documented variable airflow obstruction. Second, owing to its cross-sectional design, the effect of treatment on changes of airway-wall thickness was not explored. Third, bias may have occurred because a semi-quantitative measurement of RB1 morphology and scoring of BWT_r and AT_{exp} were conducted manually. Whole-lung measurement was not utilized, so the most clearly visible CT slice at the right apical bronchus and from the 12 dispersed lung zones was chosen judiciously to mitigate bias according to a report by Suwatanapongched *et al*.[17] CT software for quantitative analyses is recommended, but more time and specialized software are required, which may be inaccessible in resource-limited countries.

Conclusions

Asthma patients with FAO had a smaller LA and higher resistance of the proximal airways than those in COPD patients. Besides FEV_1, respiratory impedance correlated with the RB1-WA and wall thickness of the peripheral airways in asthma and with AT_{exp} in COPD.

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Conflicts of interest

There are no conflicts of interest.

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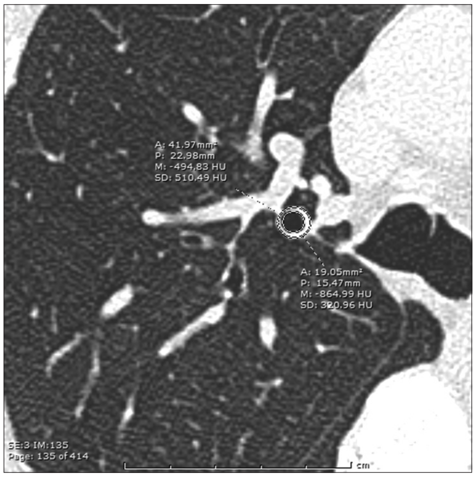
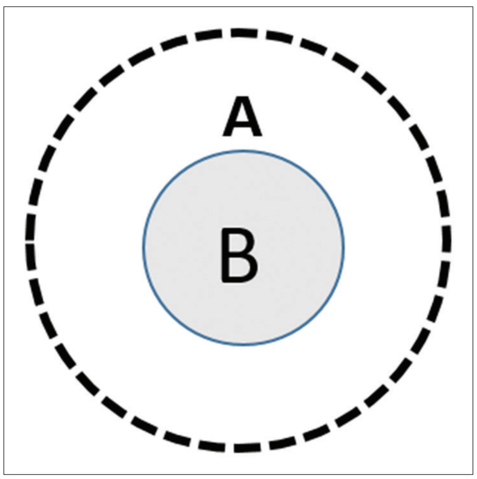
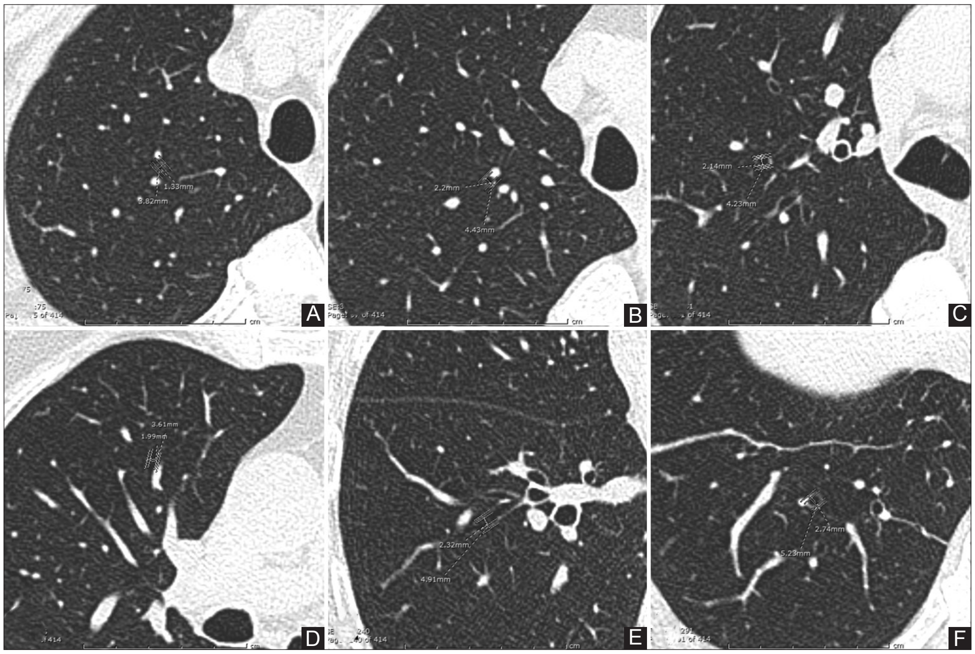


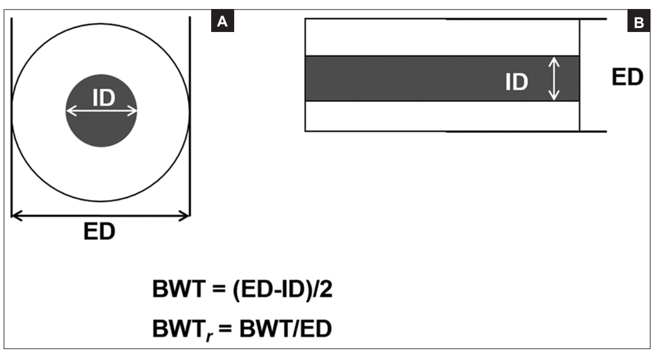
Supplement 1a: Representative axial inspiratory HRCT images for the measurement of the RB1 morphology



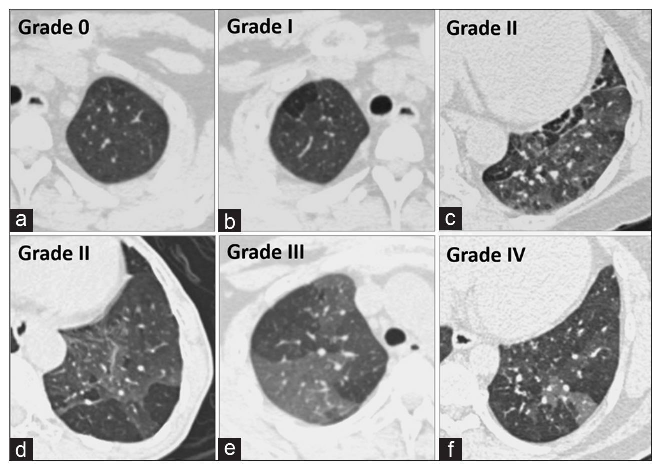
Supplement 1b: Diagram showing the total area (RB1-TA) and lumen area (RB1-LA) of the RB1. The area between the external perimeter (dashed line) and the internal perimeter (solid line) is considered RB1-TA (A). The area inner to the internal perimeter (solid line) is considered RB1-LA (B)



Supplement 2a: Representative axial inspiratory HRCT images of the thickest peripheral bronchi in the six anatomic zones. For the measurement of bronchial wall thickening (BWT). (A) Zone 1, between the apex and the crossing left brachiocephalic vein; (B) Zone 2, below zone 1 to the mid-aortic arch; (C) Zone 3, below zone 2 to the carina; (D) Zone 4, below zone 3 to 1 cm below the origin of the right bronchus intermedius; (E) Zone 5, below zone 4 to the right inferior pulmonary vein; and (F) Zone 6, below zone 5 to 1 cm below the right hemidiaphragm dome



Supplement 2b: Diagrams showing the measurement of internal diameter (ID) and external diameter (ED) of the perpendicular bronchus (A) and transversely/obliquely oriented bronchus (B) and how to calculate bronchial wall thickeness (BWT) and relative BWT (BWTr) of the 4th to 6th generation bronchi



Supplement 3: Representative axial expiratory HRCT images of the lungs showing a 5-point scale of expiratory air trapping. A. Grade 0, no ATexp; B. Grade I ≤25%; C and D. Grade II, >25-50%; E. Grade III, >50-75%; and F. Grade IV >75% of the cross-sectional area at the corresponding level