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Expiratory air trapping during asthma exacerbation: Relationships with clinical indices and proximal airway morphology

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ABSTRACT

Objectives: To semi-quantitatively assess expiratory air trapping (AT_{exp}) and structural changes in the proximal airways in asthma during asthma exacerbation (AE) and to explore the relationships among AT_{exp}, clinical indices, and proximal airway changes.

Methods: Paired inspiratory-dynamic forced expiratory CT scans of 36 asthmatics (30 women, 6 men; mean age, 49.2 ± 18.9 years) performed during AE were retrospectively reviewed for the total AT_{exp} score (summed scores [extent grading (0–4) × pattern grading (1–4)] of the twelve lung zones), morphologic parameters and expiratory bronchial collapse (BC_{exp}) of the proximal airways. The relationships of the score with clinical indices and proximal airway morphology (normalized by body surface area [BSA]) were analyzed. A *p* value of <0.05 was considered statistically significant.

Results: The mean total AT_{exp} score was 110.1 ± 43.4 (range, 8–166). It was higher in the lower zones and in patients older than 60 years, having BMI of <27.5 kg/m², and peak expiratory flow rate (PEFR) of <60% predicted. Correlation existed between the score and age (*r* = 0.331), BMI (*r* = −0.375), BSA (*r* = −0.442), % predicted PEFR (*r* = −0.332), right upper lobe apical segmental bronchus (RB1)-wall area (WA)/BSA (*r* = 0.467), %RB1-WA (*r* = 0.395), and RB1-bronchial wall thickness (BWT)/BSA (*r* = 0.378). The score showed no correlation with BC_{exp} and other morphologic bronchial parameters. Area under receiver-operating-characteristic curve 0.724 (95% CI) showed that the score of 110 could discriminate patients with PEFR of <60% predicted from those with PEFR of ≥60% predicted.

Conclusion: During AE, there was a high prevalence of extensive AT_{exp} which was correlated with patient's age, BMI, BSA, AE severity and RB1 morphology but not correlated with BC_{exp}.

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1. Introduction

Despite a deeper understanding and greater knowledge of the pathology and management of asthma, the disease remains inadequately controlled on currently available therapies in some patients

[1]. Frequent asthma exacerbation (AE) accounts for high personal and social healthcare burdens and poses the risk of long-term respiratory impairment and disability. In recent decades, there is evidence supporting the contribution of small airway dysfunction (SAD) to pathophysiology and clinical manifestations of asthma [1–3]. SAD has been found to be associated with a particular and more severe phenotype of asthma. However, it remains unclear whether there is a link between AE severity and SAD. Novel asthma therapies targeting small airways might provide clinical benefit to asthmatics who have prevalent SAD during AE [1,2,4–7].

At present, assessment of SAD remains relatively challenging. Commonly employed spirometric tests, for example, generally reflect function of the large airways and loss of lung elastic recoil [1]. Impulse oscillometry (IOS) is gaining greater importance as a non-invasive test for assessment of both peripheral and proximal airway dysfunction in adult and pediatric asthma but only provides physiologic data [1]. Most approaches to biologic assessment of the small

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airways are still under investigation and are not easy to perform in routine clinical practice [1,6].

Evidence in recent decades suggest that CT scan has emerged as a useful non-invasive tool for assessment of SAD that is not readily captured by physiologic measures [2–4,6,8,9]. CT has also been used to define asthmatic phenotypes and to help identify a group of individuals who might be at risk of severe disease. The cardinal CT sign of peripheral or small airway obstruction is generally defined by the presence of expiratory air trapping (AT_{exp}), i.e., an abnormal retention of air in all or parts of the lungs at any stage of expiration [2,9,10]. On CT, AT_{exp} can be quantified by the visual score [11] or by the densitometric analysis [3,12]. Recently, computer-assisted 3-dimensional analysis of the bronchial tree structure has enabled the quantification of morphology of the proximal airways [1–4,8,13–15]. However, such dedicated software is currently unavailable in many countries, including Thailand, which limits their use from a research perspective. Quantitative CT assessment of airway abnormalities in asthmatics on the basis of visual estimation and manual measurement has been shown to be effective and has provided strong correlations between visually scored AT_{exp} and morphologic changes in the proximal airways with pulmonary function [9–11,16].

Although there is extensive research on CT assessment of airway abnormalities in asthma [1–4,8,13–15], CT data on SAD and morphologic changes in the proximal airways during AE are still limited. It is largely unknown in what proportion of asthmatics with AE will have AT_{exp} and whether AT_{exp} will be related to the structural changes in the proximal airways. Therefore, this study was undertaken to quantify the presence of AT_{exp} during AE and the structural changes in the proximal airways, e.g., expiratory collapse of the proximal bronchi (BC_{exp}), on the basis of paired inspiratory and dynamic forced expiratory CT scans. Our secondary aim was to assess the relationships among airway abnormalities and clinical indices. By measuring the amount of AT_{exp} and changes in the proximal airways, CT may help clarify the complexity of AE, identify the at-risk asthma phenotype, and evaluate the possibility of individualized therapeutic decision during AE [1–4].

2. Materials and methods

2.1. Patients studied

This retrospective study included 36 asthma patients (aged ≥ 18 years) presenting with AE between May 2012 and December 2012. All of them had been previously enrolled in a prospective study approved by the Local Ethic Committee on Human Rights related to research involving human subjects at our institution. All of the patients provided written informed consent for the aforementioned prospective study and for future retrospective studies. All the patients fulfilled diagnostic criteria of asthma published by Global Strategy for Asthma Management and Prevention, GINA 2012 update (Available from: <http://www.ginasthma.org/>) [17]. None of the female patients were pregnant (based on date of last menstrual period and a urine pregnancy test).

The patient's demographic data (sex, age, body height, body weight), smoking habit, status of asthma and severity of AE were reviewed. Peak expiratory flow rate (PEFR) was used as the primary determinant of AE severity, based on recommendations issued in GINA 2012 [17].

2.2. Chest CT examination

2.2.1. Scanning protocol

All CT scans were performed on a 64-detector CT scanner (Aquilion TM/CX, Toshiba Medical Systems, Japan) installed in our Emergency Department.

Prior to CT scanning, all the patients received bronchodilators for initial treatment for their AE until their clinical status was stable and they were able to lie supine. The patient was then transferred to the CT room and peak flow measurement was obtained approximately 5 min prior to the CT scanning using a Mini-Wright peak flow meter (Clement Clarke International Ltd., United Kingdom).

Each patient was taught how to perform full suspended inspiration (taking a deep breath and holding it throughout the scan) and how to perform forced dynamic expiration (taking a deep breath and blowing it out without holding throughout the scan).

Helical CT scanning was performed in the craniocaudal direction for both end-inspiratory and dynamic forced expiratory images from the lung apices to approximately 1 cm below the right hemidiaphragm dome. The craniocaudal scanning length varied depending on the patient's lung height. The images were acquired with 64 detectors $\times$ 0.5 mm collimation, a gantry rotation time of 0.5 s, and a pitch factor of 1.484 (helical pitch/number of slices scanned in a single rotation). End-inspiratory CT scan was obtained first using a tube voltage of 120 kVp and a tube current of 120–200 mA (adjusted to the patient's body mass index (BMI)). Dynamic forced expiratory CT scanning was subsequently obtained and was coordinated with the onset of the patient's expiratory effort, using a tube voltage of 120 kVp and a tube current of 30 or 40 mAs. Images were reconstructed by using low (FC08) and high (FC52) spatial frequency algorithms and Quantum Denoising Software with a section thickness of 2 mm. The iterative reconstruction algorithm was not used. Images were transferred to the picture archiving and communications system (Synapse version 4.2.300; Fujifilm Medical Systems, USA), based on DICOM conformance, and were viewed on a high-resolution LED monitor (Coronis Fusion 6MP LED (MDCC-6130), Barco limited, Hong Kong). Image interpretation was performed using window width of 1600 Hounsfield units (HU) and window level of -550 HU.

2.2.2. CT assessment

A chest radiologist with 17 years of experience in chest CT and a senior radiology resident, both of whom were blinded to other clinical data, separately reviewed all CT images in a randomized order to decrease the potential for bias. The final results reached by consensus were used for statistical analysis.

2.2.2.1. Visual assessment of expiratory air trapping (AT_{exp}). The dynamic forced expiratory and end-inspiratory CT images from each examination were compared for evidence of air trapping at the 6 following anatomic levels: level 1, the crossing left brachiocephalic vein; level 2, the mid aortic arch; level 3, the carina; level 4, 1 cm below the origin of the right bronchus intermedius; level 5, the right inferior pulmonary vein; and level 6, 1 cm below the right hemidiaphragm dome.

AT_{exp} was considered present when a lung region exhibited a less-than-normal increase in attenuation and a lack of change in volume during expiration when compared to the appearance of that lung region on the paired end-inspiratory CT images [18,19]. The extent and pattern of AT_{exp} were adapted from previous studies [10,18,19]. The extent of AT_{exp} (Fig. 1) was graded on a 5-point scale: 0, no visible AT_{exp} ; I, 1–25%; II, 26–50%; III, 51–75%; and IV, 76–100% of the cross-sectional area of each lung zone [18,19]. The pattern of AT_{exp} in each lung zone (Fig. 1) was categorized as (1) small areas of air trapping corresponding to one or two adjacent secondary pulmonary lobules; (2) three or more areas of lobular air trapping; (3) subsegmental air trapping; and 4, diffuse air trapping (contiguous area of air trapping larger than subsegmental in distribution) [18,19].

We scored the extent and pattern of AT_{exp} in each of the 12 lung zones. The AT_{exp} score in each zone was subsequently derived by multiplying the extent grading with pattern grading in each lung

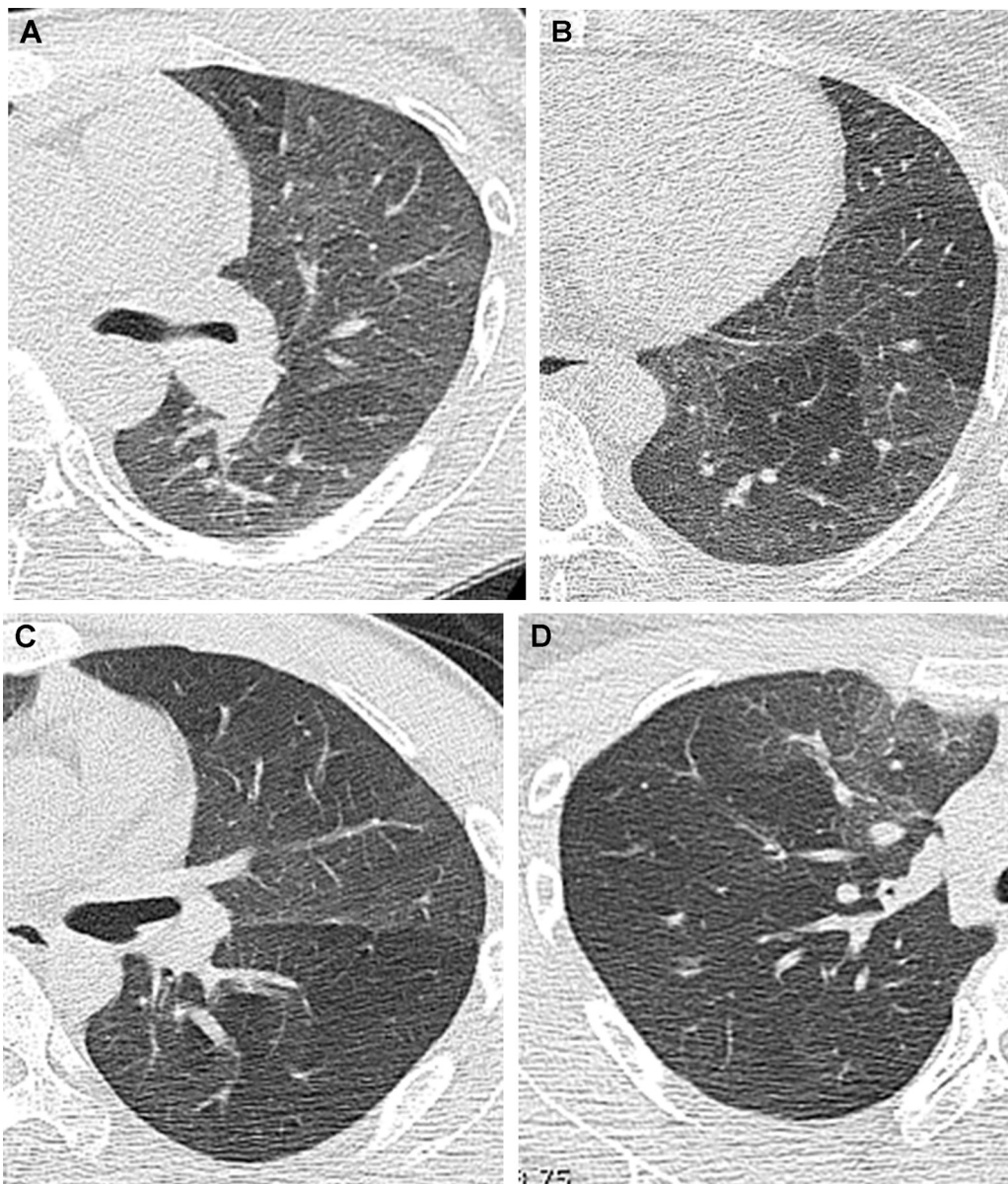


Fig. 1. Dynamic forced expiratory CT images and AT_{exp} score in asthma patients.

(a) Axial CT at the level 4 (1 cm below the origin of the right bronchus intermedius) in a 21-year-old female patient showing AT_{exp} score of 1 (extent grading of 1 $\times$ pattern grading of 1) in the left lung zone. (b) Axial CT at the level 6 (1 cm below the right hemidiaphragm dome) in a 37-year-old female patient showing AT_{exp} score of 2 (extent grading of 1 $\times$ pattern grading of 2) in the left lung zone. (c) Axial CT at the level 4 in a 20-year-old female patient showing AT_{exp} score of 9 (extent grading of 3 $\times$ pattern grading of 3) in the left lung zone. (d) Axial CT at the level 3 (carina) in a 21-year-old female patient showing AT_{exp} score of 16 (extent grading of 4 $\times$ pattern grading of 4) in the right lung zone.

zone. The summed score of the AT_{exp} scores in the 12 lung zones was considered the total AT_{exp} scores (maximum possible score of 192) and was used for the analysis.

2.2.2.2. Assessment of changes in the proximal airways. Changes in the proximal airways were determined in terms of expiratory collapse (BC_{exp}) and morphological parameters. All the measurements were done manually using an electronic outlining tool. Each was done twice to obtain an average value for the analysis.

We evaluated BC_{exp} of the bronchi that was oriented perpendicular to the image plane, i.e., right bronchus intermedius (BI), the right basal trunk (RBT), the left basal trunk (LBT), and the right upper lobe apical segmental bronchus (RB1). All measurements of the RB1 morphology were done at the level where its external

perimeter was clearly visible [8,13,15]. The external perimeter of the RB1 was considered the total area (RB1-TA) (Fig. 2).

The areas within the internal perimeter of each bronchus at inspiration and expiration were considered inspiratory luminal area (LA) and expiratory luminal area (LA_{exp}), respectively, of that bronchus. The presence and degree of bronchial collapse (BC_{exp}) were calculated as a percentage of the reduction in the LA_{exp} of the bronchus relative to the LA at the same anatomic level, i.e., $BC_{exp} = 100 \times (LA - LA_{exp})/LA$. BC_{exp} was considered to be present when the bronchus exhibited a reduction $>50\%$ in its LA_{exp} [18,21]. When present, BC_{exp} was further categorized as mild ($>50\text{--}70\%$), moderate ($>70\text{--}90\%$), and severe ($>90\%$) collapse.

Other morphologic parameters of the RB1 on the inspiratory CT scan were also determined. The wall area of the RB1 (RB1-WA) was calculated by subtracting the RB1-TA from the RB1-LA. The

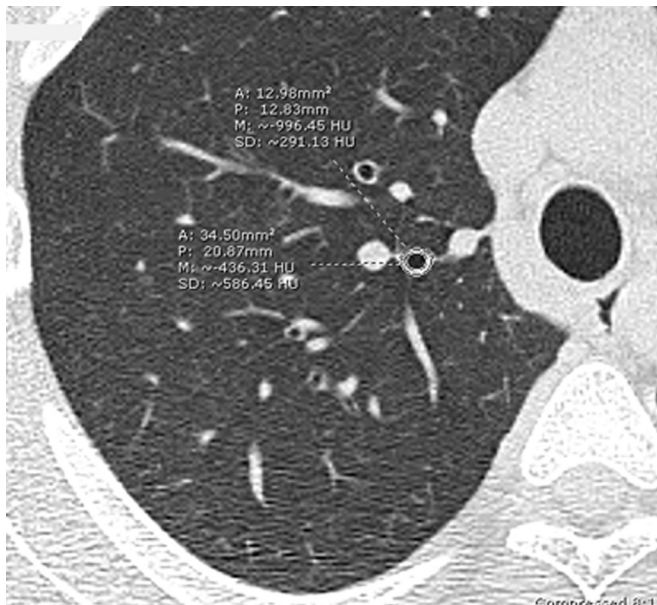


Fig. 2. Representative thin-section axial CT image in a patient with asthma. The measurements of the internal and external perimeters of the right upper lobe apical segmental bronchus (RB1) using an electronic outlining tool are presented.

percentage of RB1-WA (%RB1-WA) was calculated by the following formula: $(\%RB1-WA = 100 \times (RB1-WA/RB1-TA))$. The RB1-WA/LA was also calculated.

The long-axis and short-axis lengths of the external and internal diameters of the RB1 were also measured. The mean diameter was defined as the average of long-axis and short-axis diameters of the RB1.

Bronchial wall thickness of the RB1 was then calculated by two formulas; (1) subtracting the long-axis internal diameter of the RB1 from its long-axis external diameter divided by two ($RB1-BWT_{LD}$) and (2) subtracting the mean internal diameter of the RB1 from its mean external diameter divided by two ($RB1-BWT_{MD}$). The percentages of RB1-BWT based on its long-axis diameter ($\%RB1-BWT_{LD}$) and its mean diameter ($\%RB1-BWT_{MD}$) were subsequently calculated by the following formulas: $100 \times (RB1-BWT_{LD}/RB1_{LD})$ and $100 \times (RB1-BWT_{MD}/RB1_{MD})$, respectively.

The LA and LA_{exp} of all bronchi being evaluated and the other morphologic parameters of the RB1 were subsequently normalized by body surface area (BSA, m^2), based on DuBois formula.

2.3. Statistical analysis

All statistical analyses were done using STATA® software version 13 (Stata Corporation, Texas, USA).

The interobserver agreements of the pattern and extent of AT_{exp} between the two observers were tested using weighted κ statistics. A κ value between 0.00 and 0.20, 0.21 and 0.40, 0.41 and 0.60, 0.61 and 0.80, and 0.81 and 1.00 were considered to indicate poor agreement, fair agreement, moderate agreement, good agreement and very good agreement, respectively.

The patients' characteristics, AT_{exp} , and morphologic parameters of the proximal airways were presented in terms of a mean $\pm$ standard deviation (SD) and range. The correlations of the total AT_{exp} scores with clinical indices, BC_{exp} and morphologic bronchial parameters were analyzed using Pearson correlation coefficient or Spearman rank correlation coefficient as appropriate. Because there is evidence that suggests that asthma severity may be associated with gender, age and weight [20,22,23] and that AT_{exp} may be associated with BC_{exp} [19], we performed subgroup analysis

Table 1

Asthma status and severity of the 36 asthma patients.

GINA ^a	n (%)
Status of asthma	
Controlled	4 (11.1)
Partially controlled	24 (66.7)
Uncontrolled	8 (22.2)
Severity of asthma exacerbation	
Mild	1 (2.8)
Moderate	8 (22.2)
Severe	27 (75.0)

^a According to Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, GINA 2012 update. Available from: <http://www.ginasthma.org/> Accessed November 12, 2012 [17].

Table 2

Correlations of the total AT_{exp} score with clinical indices.

Clinical characteristics (n = 36)	Mean $\pm$ SD	Range	Correlation with total AT_{exp} score	
			$r^{\dagger}$	p^*
Age (years)	49.2 $\pm$ 18.9	18–83	0.331	0.049
Body height (cm)	157.3 $\pm$ 8.9	135–176	−0.183	0.285
Body weight (kg)	61.7 $\pm$ 10.5	43–78	−0.478	0.003
BMI (kg/m^2)	25.0 $\pm$ 4.2	17.4–32.6	−0.375	0.024
BSA (m^2)	1.61 $\pm$ 0.15	1.33–1.91	−0.442	0.007
%predicted PEFR during AE	58.5 $\pm$ 16.5	22.7–86.7	−0.332	0.048

Abbreviations: SD—standard deviation; AT_{exp} —expiratory air trapping; BMI—body mass index; BSA—body surface area; PEFR—peak expiratory flow rate; AE—asthma exacerbation.

[†] Pearson correlation.

* A p value of $p < 0.05$ is considered statistically significant.

of the total AT_{exp} scores and/or morphologic bronchial parameters on the basis of gender, age (≤ 60 years and > 60 years), BMI ($< 27.5 kg/m^2$ and $\geq 27.5 kg/m^2$), %predicted PEFR ($\geq 60\%$ and $< 60\%$ of the predicted value), and the presence or absence of BC_{exp} . The age threshold was chosen based on a previous study by Yilmaz et al. [20], while the BMI threshold was chosen based on a WHO Expert Consultation in 2004 that identified a BMI $\geq 27.5 kg/m^2$ as being in the high risk range for Asian populations [24]. The %predicted PEFR threshold of $< 60\%$ was chosen because it is one of the criteria for defining severe AE in GINA 2012 [17]. A two-tailed t test or a Mann–Whitney U test was used for comparison as appropriate. A p value of < 0.05 was considered to indicate statistically significant.

A receiver operating characteristic (ROC) analysis was then applied to assess the performance of the total AT_{exp} score in discriminating patients having PEFR $< 60\%$ of predicted value from those with PEFR $\geq 60\%$ of predicted value.

3. Results

3.1. Clinical indices

Of the 36 patients, 30 (83.3%) patients were women, and 6 (16.7%) were men. All the patients were never-smoked. Using the GINA 2012 definitions [17], the majority of the patients had partially controlled asthma and had severe AE (Table 1). Other clinical indices of the patients are summarized in Table 2. Twenty two (61.1%) and 14 (38.9%) patients had PEFR $\geq 60\%$ and $< 60\%$ of predicted value, respectively (Table 3).

3.2. CT findings

All end-inspiratory and dynamic forced expiratory volumetric CT examinations of the 36 patients were of diagnostic quality. One of the patients had extensive mucus plugging causing complete occlusion of all bronchi in the right upper lobe, hence precluding the

Table 3Comparison of the total AT_{exp} scores and morphologic parameters of the RB1 between the two subgroups based on age, BMI and %predicted PEFR.

	Age ≤ 60 years	Age > 60 years	$p^{\dagger \ddagger}$	BMI < 27.5 kg/m ²	BMI ≥ 27.5 kg/m ²	$p^{\dagger \ddagger}$	PEFR $\geq 60\%$ predicted	PEFR $< 60\%$ predicted	$p^{\dagger \ddagger}$
Number of patients (n = 36)	25	11		25	11		22	14	
Total AT_{exp} scores	99.5 $\pm$ 41.4	134.3 $\pm$ 39.5	0.025	121.8 $\pm$ 38.8	83.6 $\pm$ 43.4	0.013	97.0 $\pm$ 48.6	130.8 $\pm$ 22.7	0.023
Number of patients (n = 35)	24	11		25	10		21	14	
End-inspiratory CT									
RB1-WA (mm ²)	21.5 $\pm$ 6.3	23.0 $\pm$ 7.7	0.548	22.1 $\pm$ 6.7	21.8 $\pm$ 7.1	0.922	21.1 $\pm$ 6.1	23.4 $\pm$ 7.5	0.312
RB1-WA/BSA (mm ² /m ²)	13.2 $\pm$ 4.2	15.1 $\pm$ 5.2	0.254	14.2 $\pm$ 4.7	12.7 $\pm$ 4.2	0.370	12.7 $\pm$ 3.8	15.3 $\pm$ 5.3	0.103
%RB1-WA	61.0 $\pm$ 7.2	62.2 $\pm$ 11.4	0.697	61.7 $\pm$ 9.2	60.4 $\pm$ 6.9	0.689	59.7 $\pm$ 6.5	63.9 $\pm$ 10.7	0.161
RB1-BWT _{LD} (mm)	1.2 $\pm$ 0.3	1.3 $\pm$ 0.3	0.697	1.3 $\pm$ 0.3	1.3 $\pm$ 0.4	0.898	1.3 $\pm$ 0.3	1.2 $\pm$ 0.3	0.709
RB1-BWT _{LD} /BSA	0.8 $\pm$ 0.2	0.9 $\pm$ 0.2	0.232	0.8 $\pm$ 0.2	0.7 $\pm$ 0.2	0.365	0.8 $\pm$ 0.2	0.8 $\pm$ 0.2	0.614
%RB1-BWT _{LD}	35.0 $\pm$ 6.8	36.3 $\pm$ 8.9	0.631	35.6 $\pm$ 7.7	34.8 $\pm$ 7.0	0.766	35.6 $\pm$ 7.2	35.1 $\pm$ 8.0	0.849
RB1-BWT _{MD} (mm)	1.2 $\pm$ 0.3	1.2 $\pm$ 0.4	0.799	1.2 $\pm$ 0.3	1.2 $\pm$ 0.4	0.833	1.2 $\pm$ 0.3	1.2 $\pm$ 0.4	0.629
RB1-BWT _{MD} /BSA	0.7 $\pm$ 0.2	0.8 $\pm$ 0.3	0.556	0.8 $\pm$ 0.2	0.7 $\pm$ 0.2	0.209	0.8 $\pm$ 0.2	0.8 $\pm$ 0.3	0.671
RB1-LA (mm ²)	13.8 $\pm$ 4.5	13.8 $\pm$ 6.5	0.968	13.8 $\pm$ 5.8	13.8 $\pm$ 2.8	0.983	14.0 $\pm$ 4.3	13.4 $\pm$ 6.3	0.724
RB1-LA/BSA (mm ² /m ²)	8.4 $\pm$ 2.8	9.1 $\pm$ 4.7	0.915 [†]	8.9 $\pm$ 3.9	8.0 $\pm$ 1.6	0.496	8.5 $\pm$ 2.6	8.8 $\pm$ 4.5	0.762 [†]
RB1-TA (mm ²)	35.3 $\pm$ 9.2	36.9 $\pm$ 11.5	0.667	35.9 $\pm$ 10.6	35.6 $\pm$ 8.1	0.938	35.1 $\pm$ 9.2	36.8 $\pm$ 11.0	0.614
RB1-TA/BSA (mm ² /m ²)	21.6 $\pm$ 6.1	24.2 $\pm$ 8.1	0.289	23.1 $\pm$ 7.3	20.6 $\pm$ 4.8	0.338	21.3 $\pm$ 5.7	24.1 $\pm$ 8.0	0.229
Forced-expiratory CT									
RB1-LA _{exp} (mm ²)	5.3 $\pm$ 4.5	5.4 $\pm$ 4.0	0.887	6.3 $\pm$ 4.5	2.9 $\pm$ 2.6	0.024 [†]	5.5 $\pm$ 4.4	5.0 $\pm$ 4.3	0.567
RB1-LA _{exp} /BSA (mm ² /m ²)	3.2 $\pm$ 2.9	3.6 $\pm$ 2.7	0.696	4.0 $\pm$ 2.9	1.7 $\pm$ 1.6	0.014 [†]	3.41 $\pm$ 2.9	3.2 $\pm$ 2.8	0.814

Data presented as mean $\pm$ standard deviation (SD).Abbreviations: AT_{exp} —expiratory air trapping; BMI—body mass index; BSA—body surface area; PEFR—peak expiratory flow rate; RB1—right upper lobe apical segmental bronchus; WA—wall area; BWT_{LD}—bronchial wall thickening based on long axis diameter; BWT_{MD}—bronchial wall thickening based on mean diameter; LA—inspiratory luminal area; TA—total area; LA_{exp}—expiratory luminal area.[†] Comparison between two subgroups using two tailed *t* test, unless otherwise stated.[‡] Comparison between two subgroups using Mann–Whitney *U* test.^{*} A *p* value of < 0.05 is considered statistically significant.

assessment of her RB1. Despite having a tracheal bronchus in one patient, the segmental branching pattern arising from the tracheal bronchus was normal. Hence, AT_{exp} and BC_{exp} , LA and LA_{exp} of the BI, RBT and LBT were based on the 36 patients, while the BC_{exp} and morphologic parameters of the RB1 were based only on 35 patients.

3.2.1. AT_{exp} and its relationships with clinical indices

AT_{exp} was detected in all the 36 (100%) patients during AE. The mean total AT_{exp} score was 110.1 ± 43.4 (range, 6–188). The mean total AT_{exp} scores for the 6 CT levels were 15.9 ± 10.6 for level 1, 16.6 ± 9.2 for level 2, 16.4 ± 9.4 for level 3, 18.1 ± 9.1 for level 4, 19.4 ± 8.2 for level 5 and, 23.6 ± 8.5 for level 6. The summed AT_{exp} score of 61.3 ± 20.5 in the lower lung zone (levels 4–6) was significantly higher than that of 48.7 ± 27.6 in the upper lung zone (levels 1–3) ($p = 0.002$).

All the patients had combined patterns of AT_{exp} , namely patterns 3 and 4 in 29 (80.6%) patients, patterns 1 and 3 in 4 (11.1%) patients, and patterns 2 and 4 in 3 (8.3%) patients. The extent of AT_{exp} was 1–25%, 26–50%, 51–75%, and 76–100% in 1 (2.8%) patient, 1 (2.8%) patient, 5 (13.9%) patients and 29 (80.5%) patients, respectively. There was good and very good agreement (κ values, 0.72–0.88) between the two observers in grading the pattern and extent of AT_{exp} .

The total AT_{exp} scores in female (110.8 ± 44.5) and male (106.7 ± 41.2) subjects were not statistically different ($p = 0.834$). As shown in Tables 2 and 3, the total AT_{exp} score was significantly correlated with age and was significantly higher in the > 60 years of age subgroup. Meanwhile, there was negative correlation between the total AT_{exp} score and BMI. Patients having BMI of < 27.5 kg/m² had higher total AT_{exp} scores than did those having BMI of ≥ 27.5 kg/m².

We also found that patients with severe AE (mean $\pm$ SD, 120.2 ± 37.0) had a higher total AT_{exp} score than did those with mild and moderate AE (mean $\pm$ SD, 92.6 ± 44.0), but statistical significance was not achieved ($p = 0.074$). Based on %predicted PEFR (Table 3), however, patients with PEFR $< 60\%$ of predicted value had a significantly higher total AT_{exp} score than those with PEFR $\geq 60\%$ of predicted value. As illustrated in Fig. 3, the area under ROC analysis of the total AT_{exp} score and %predicted PEFR was 0.724 (Youden

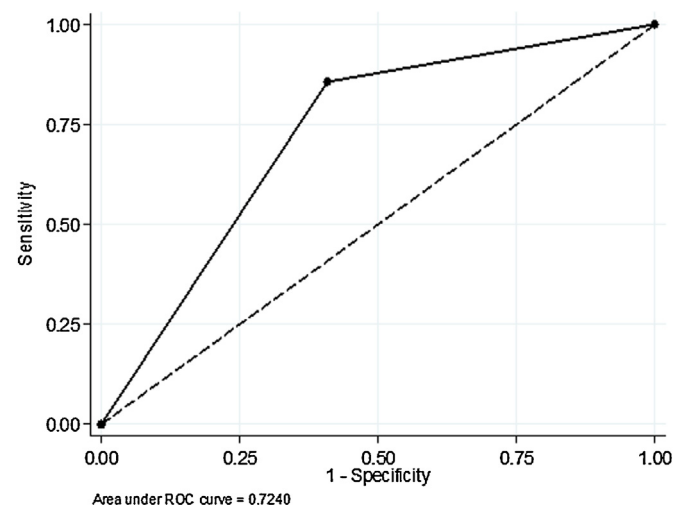


Fig. 3. Illustration of ROC analysis showing that the area under curve of the total AT_{exp} scores and %predicted PEFR is 0.724 (Youden index, 95% CI: 0.582–0.866).

index, 95% CI: 0.582–0.866). This suggested that the cut-off value of the total AT_{exp} score of 110 could discriminate patients having PEFR $< 60\%$ of predicted value from those having PEFR $\geq 60\%$ of predicted value, with a sensitivity of 92.9% and a specificity of 59.1%.

3.2.2. Expiratory collapse and morphology of the proximal airways and their relationships with the total AT_{exp} score

Irrespective of anatomic locations, BC_{exp} was found in 75% of asthma patients during AE. Approximately one third of the patients had moderate-degree BC_{exp} of the BI, RBT, LBT, and RB1 (Table 4). As shown in Table 5, the degree of BC_{exp} of all bronchi was not correlated with the total AT_{exp} score and %predicted PEFR, and there was no significant difference in the total AT_{exp} score in patients with BC_{exp} and without BC_{exp} .

Various morphologic parameters of the RB1 and their relationships with the total AT_{exp} scores and clinical indices are in

Table 4

The frequencies and severity of expiratory bronchial collapse (BC_{exp}) during asthma exacerbation.

Bronchi (n = 36)	No BC _{exp}		Degree of BC _{exp}					
	≤50%		>50–70%		>70–90%		>90%	
	n	%	n	%	n	%	n	%
BI	18	50.0	7	19.4	11	30.6	0	0
RBT	9	25.0	10	27.8	13	36.1	4	11.1
LBT	12	33.3	9	25.0	12	33.3	3	8.3
RB1 ^a	11	31.4	8	22.9	13	37.1	3	8.6

Abbreviations: BC_{exp}—expiratory bronchial collapse; BI—right bronchus intermedius, RBT—right basal trunk; LBT—left basal trunk; RB1—right upper lobe apical segmental bronchus.

^a Based on 35 patients.

Tables 3 and 6. As shown in Table 3, the RB1-LA_{exp} and RB1-LA_{exp}/BSA were significantly smaller in the subgroup with BMI <27.5 kg/m² than in the subgroup with BMI ≥27.5 kg/m². In Table 6, the total AT_{exp} score showed significant correlation with RB1-WA, RB1-WA/BSA, %RB1-WA, RB1-BWT_{LD}/BSA, RB1-BWT_{MD}/BSA, and

RB1-WA/LA. RB1-TA/BSA showed a borderline significance with the total AT_{exp} score ($p = 0.055$).

In addition, RBT-LA was significantly smaller in the subgroup with PEFR <60% of predicted value (mean ± SD, 35.2 ± 14.0) than did in the subgroup with PEFR ≥60% of predicted value (mean ± SD, 44.3 ± 11.7) ($p = 0.042$). RBT-LA_{exp} was larger in the subgroup with BMI <27.5 kg/m² (mean ± SD, 11.3 ± 7.5) than those with BMI ≥27.5 kg/m² (mean ± SD, 6.7 ± 5.1), and RBT-LA_{exp}/BSA correlated with the total AT_{exp} score ($r = 0.286$). But the mean difference ($p = 0.077$) and correlation ($p = 0.091$) were not significant.

There were no significant correlations between the total AT_{exp} score and other morphologic parameters of the RB1, BI, RBT and LBT. These morphologic parameters showed no correlations with %predicted PEFR and were similar in the two subgroups based on age, BMI and %predicted PEFR.

4. Discussion

Our study established that there was a high prevalence of extensive AT_{exp} during AE. Unlike the prior study that did not find zonal predominance [8], we found lower-zone predominant AT_{exp}. Our

Table 5

Relationships between the total AT_{exp} score and BC_{exp} during asthma exacerbation.

Bronchi (n = 36)	Patients without BC _{exp}		Patients with BC _{exp}		Comparison [†]	Pearson correlation between the total AT _{exp} score and %BC _{exp}	
	n (%)	Total AT _{exp} score (mean ± SD)	n (%)	Total AT _{exp} score (mean ± SD)		r	p [*]
BI	18 (54.5)	110.4 ± 46.5	18 (50.0)	109.8 ± 41.4	0.967	0.054	0.755
RBT	9 (25.0)	112.4 ± 37.4	27 (75.0)	109.4 ± 45.9	0.857	−0.201	0.239
LBT	12 (33.3)	118.4 ± 36.4	24 (66.7)	106.0 ± 46.7	0.427	−0.068	0.692
RB1 ^a	11 (31.4)	123.0 ± 41.5	24 (68.6)	104.1 ± 44.7	0.286 [‡]	−0.150	0.389

Abbreviations: AT_{exp}—expiratory air trapping; BC_{exp}—expiratory bronchial collapse; BI—right bronchus intermedius, RBT—right basal trunk; LBT—left basal trunk; RB1—right upper lobe apical segmental bronchus; SD—standard deviation.

^a Based on 35 patients.

[†] Comparison between two subgroups using two tailed *t* test, unless otherwise stated.

[‡] Comparison between two subgroups using Mann–Whitney *U* test.

^{*} A *p* value of <0.05 is considered statistically significant.

Table 6

Correlations of the total AT_{exp} score and %predicted PEFR with morphologic parameters of the RB1.

Morphologic parameters (n = 35)	Mean ± SD	Range	Correlation [†]			
			Total AT _{exp} score		%predicted PEFR	
			r	p [*]	r	p [*]
End-inspiratory CT						
RB1-WA (mm ²)	22.0 ± 6.7	9.7–36.4	0.354	0.037	−0.096	0.584
RB1-WA/BSA (mm ² /m ²)	13.8 ± 4.6	5.8–25.7	0.467	0.005	−0.146	0.401
%RB1-WA	61.4 ± 8.6	46.4–81.3	0.395	0.019	−0.178	0.306
RB1-BWT _{LD} (mm)	1.3 ± 0.3	0.6–2.0	0.215	0.215	−0.005	0.979
RB1-BWT _{LD} /BSA	0.8 ± 0.2	0.3–1.2	0.378	0.025	−0.075	0.668
%RB1-BWT _{LD}	35.4 ± 7.4	23.1–51.7	0.218	0.208	0.006	0.975
RB1-BWT _{MD} (mm)	1.2 ± 0.3	0.3–1.7	0.205	0.237	0.075	0.669
RB1-BWT _{MD} /BSA	0.7 ± 0.2	0.2–1.2	0.364	0.032	−0.009	0.961
%RB1-BWT _{MD}	37.3 ± 6.2	22.1–52.4	0.273	0.112	−0.097	0.578
RB1-LA (mm ²)	13.8 ± 5.1	4.8–31.5	−0.118	0.501	0.073	0.677
RB1-LA/BSA (mm ² /m ²)	8.6 ± 3.4	3.6–22.2	0.193	0.912	0.003	0.986
RB1-WA/LA	1.7 ± 0.7	0.9–4.4	0.376	0.026	−0.252	0.145
RB1-TA (mm ²)	35.8 ± 9.8	17.4–58.7	0.181	0.299	−0.028	0.875
RB1-TA/BSA (mm ² /m ²)	22.4 ± 6.7	10.1–41.4	0.326	0.055	−0.098	0.576
Forced-expiratory CT						
RB1-LA _{exp} (mm ²)	5.3 ± 4.3	0.1–17.4	0.114 [‡]	0.516	0.141 [‡]	0.419
RB1-LA _{exp} /BSA (mm ² /m ²)	3.3 ± 2.8	0.7–12.4	0.168 [‡]	0.335	0.092 [‡]	0.601

Abbreviations: AT_{exp}—expiratory air trapping; BSA—body surface area; PEFR—peak expiratory flow rate; RB1—right upper lobe apical segmental bronchus; WA—wall area; BWT_{LD}—bronchial wall thickening based on long axis diameter; BWT_{MD}—bronchial wall thickening based on mean diameter; LA—inspiratory luminal area; TA—total area; LA_{exp}—expiratory luminal area.

[†] Pearson correlation coefficient, unless otherwise stated.

[‡] Spearman rank correlation coefficient.

^{*} A *p* value of <0.05 is considered statistically significant.

patients with severe AE had a higher, albeit statistically insignificant, total AT_{exp} score than did those with mild to moderate AE defined by GINA 2012 [17]. Nevertheless, the total AT_{exp} score during AE was significantly higher in the subgroup with $PEFR < 60\%$ of predicted value than in the subgroup with $PEFR \geq 60\%$ of predicted value, and the total AT_{exp} score of 110 could discriminate these two subgroups. As expected, the prevalence and severity of AT_{exp} in our patients was much higher than those in uncomplicated or mild intermittent asthma [3,11,15,16,25] and in asymptomatic subjects [10]. Yet, it is important to note that the method for scoring AT_{exp} in our study differs from those in the prior studies which relied only on the extent [9,11,18,19] or pattern [16] of AT_{exp} . Our results agree with the study of Busacker et al. [12] showing that quantitative CT-determined AT_{exp} is associated with individuals at high risk of severe disease. Hence, considering both the extent and pattern of AT_{exp} seems to be appropriate.

Although the prior studies [18,19] found a higher frequency and greater severity of AT_{exp} in patients having tracheobronchomalacia, we found no correlation between the total AT_{exp} score and BC_{exp} frequently observed during AE. Unlike the study of Matsuoka et al. [26] showing close correlation between LA_{exp} of the bronchi and expiratory airflow measurement in patients with chronic obstructive pulmonary disease, we found no significant correlation of LA_{exp} of the bronchi and the total AT_{exp} score $PEFR$. Based on our study design and a high prevalence of BC_{exp} among healthy subjects study [27], it is not possible to conclude whether the BC_{exp} noted in our study was attributable to normal airway collapse, excessive dynamic airway collapse, or true bronchomalacia (secondary to weakening or destruction) of the bronchial cartilage [21] and to determine the relevance of BC_{exp} observed during AE.

We found significant correlation between the total AT_{exp} score and some morphologic parameters of the RB1 during AE. Interestingly, the RB1-WA and RB1-BWT in our study were quite comparable to those found in asthma patients with moderate AT_{exp} and those with severe AT_{exp} and bronchial luminal narrowing in the prior study [4], even though they used fully automated computer software and we used manual measurement.

Hence, based on our findings, we speculate that SAD contributes to airflow limitation, coincides with changes in the RB1, and is unrelated to BC_{exp} during AE. Without follow-up and pathological correlation, however, it remains unclear whether AT_{exp} during AE will be partially or completely reversible thereafter or whether AT_{exp} and changes in the RB1 are attributable to airway remodeling (smooth muscle thickening) or airway inflammation [3,4,13].

The total AT_{exp} score showed significant relationships with certain clinical indices. Our patients older than 60 years had a higher total AT_{exp} score than the younger patients, similar to the previous study [20,28]. Although there is evidence suggesting increased AT_{exp} with increased age, it is very unlikely that asymptomatic elderly subjects have extensive AT_{exp} with an extent of greater than 25% of the lung level being evaluated [9,16]. It is likely that the severity of AT_{exp} in our patients older than 60 years reflects a high frequency of SAD related to asthma [8,20,28].

We found negative correlation between total AT_{exp} scores and BMI, and the subgroup with $BMI \geq 27.5 \text{ kg/m}^2$ had lower total AT_{exp} scores than did the subgroup with $BMI < 27.5 \text{ kg/m}^2$, despite smaller RB1- LA_{exp} . Our results conflict with studies suggesting significant peripheral airway abnormalities in obese patients [29], but support the studies suggesting that obesity is not necessarily associated with airway obstruction, airway hyper-responsiveness, or more severe symptoms [22,23]. A reduction in lung elastance and lung recoil after weight loss in asthmatics [30] may also explain our findings. Due to complex relationships between obesity and asthma [22,23,29], the mechanism remains unclear and needs further determination.

Our study has several limitations. First, the sample size was small because only stable patients with AE could undergo CT. Second, all CT scans were obtained without spirometric control of lung volume. However, this was also a limitation in many previous studies [4,9–11,13–16,19,20], and all of our study patients were taught for proper inspiration and expiration techniques and then practiced these techniques prior to CT scan to ensure adequate inspiratory and expiratory effort. A previous study has also already shown that spirometric gating is unlikely to provide further improvement in quantitative CT repeatability [4]. Third, AT_{exp} and morphologic bronchial parameters were assessed visually and measured manually. Therefore, our analyses of the proximal airway morphology were largely based on the lumen and/or wall dimensions of the RB1, which generally reflected changes in other proximal airways in asthma [3,4,13]. We also found good to very good agreements in assessment of AT_{exp} by the two observers and our results are in line with the previous studies using fully automated computer software [1,2,4,13]. Nevertheless, reproducibility and validation of our scoring method would benefit from further research. Fourth, complete spirometric testing and IOS were not performed due to technical limitations during AE. According to GINA 2012 [17], however, %predicted $PEFR$ is a primary determinant of the severity in AE and correlates reasonably well with %predicted forced expiratory volume at one second. Finally, without pathological correlation and follow-up studies, we were not able to determine the pathology and outcome of the abnormalities observed during AE.

5. Conclusions

During AE, AT_{exp} was always present and usually extensive. The total AT_{exp} score determined by our method significantly correlated with RB1-WA, RB1-BWT, and clinical indices, but not with BC_{exp} . The threshold score of 110 for AT_{exp} could discriminate between patients with $PEFR < 60\%$ of predicted value and those having $PEFR \geq 60\%$ of predicted value. Despite some technical limitations, we believe that our findings are interesting and contribute to the relevance of AT_{exp} coinciding with the changes in RB1 morphology in AE. Our scoring method may also serve as a simple, screening tool to help assess severe or difficult-to-control asthma, identify patients with the at-risk asthma phenotype, and evaluate the possibility of novel therapies targeting small airways during AE.

Conflict of interest

All authors declare no conflict of interest.

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References

- [1] N. Scichilone, M. Contoli, D. Paleari, P. Pirina, A. Rossi, C.M. Sanguinetti, et al., Assessing and accessing the small airways: implications for asthma management, *Pulm. Pharmacol. Ther.* 26 (2) (2013) 172–179.
- [2] G. Dourmes, F. Laurent, Airway remodelling in asthma and COPD: findings, similarities, and differences using quantitative CT, *Pulm. Med.* 2012 (2012) 670414.
- [3] C. Walker, S. Gupta, R. Hartley, C.E. Brightling, Computed tomography scans in severe asthma: utility and clinical implications, *Curr. Opin. Pulm. Med.* 18 (1) (2012) 42–47.
- [4] S. Gupta, R. Hartley, U.T. Khan, A. Singapuri, B. Hargadon, W. Monteiro, et al., Quantitative computed tomography-derived clusters: redefining airway remodeling in asthmatic patients, *J. Allergy Clin. Immunol.* 133 (3) (2014) 729–738.
- [5] L. Bjermer, The role of small airway disease in asthma, *Curr. Opin. Pulm. Med.* 20 (1) (2014) 23–30.

- [6] M. van den Berge, N.H. ten Hacken, J. Cohen, W.R. Douma, D.S. Postma, Small airway disease in asthma and COPD: clinical implications, *Chest* 139 (2) (2011) 412–423.
- [7] J.R. Johnson, Q. Hamid, Appraising the small airways in asthma, *Curr. Opin. Pulm. Med.* 18 (1) (2012) 23–28.
- [8] H. Gono, K. Fujimoto, S. Kawakami, K. Kubo, Evaluation of airway wall thickness and air trapping by HRCT in asymptomatic asthma, *Eur. Respir. J.* 22 (6) (2003) 965–971.
- [9] K.W. Lee, S.Y. Chung, I. Yang, Y. Lee, E.Y. Ko, M.J. Park, Correlation of aging and smoking with air trapping at thin-section CT of the lung in asymptomatic subjects, *Radiology* 214 (3) (2000) 831–836.
- [10] N. Tanaka, T. Matsumoto, G. Miura, T. Emoto, N. Matsunaga, K. Ueda, et al., Air trapping at CT: high prevalence in asymptomatic subjects with normal pulmonary function, *Radiology* 227 (3) (2003) 776–785.
- [11] D. Chen, W.R. Webb, M.L. Storto, K.N. Lee, Assessment of air trapping using postexpiratory high-resolution computed tomography, *J. Thorac. Imaging* 13 (2) (1998) 135–143.
- [12] A. Busacker, J.D. Newell Jr., T. Keefe, E.A. Hoffman, J.C. Granroth, M. Castro, et al., A multivariate analysis of risk factors for the air-trapping asthmatic phenotype as measured by quantitative CT analysis, *Chest* 135 (1) (2009) 48–56.
- [13] R.S. Aysola, E.A. Hoffman, David S. Gierada, S. Wenzel, J. Cook-Granroth, J. Tarsi, et al., Airway remodeling measured by multidetector CT is increased in severe asthma and correlates with pathology, *Chest* 134 (6) (2008) 1183–1191.
- [14] M. Montaudon, M. Lederlin, S. Reich, H. Begueret, J.M. Tunon-de-Lara, R. Marthan, 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* 253 (3) (2009) 844–853.
- [15] A. Niimi, H. Matsumoto, R. Amitani, Y. Nakano, M. Mishima, M. Minakuchi, et al., Airway wall thickness in asthma assessed by computed tomography. Relation to clinical indices, *Am. J. Respir. Crit. Care Med.* 162 (4) (2000) 1518–1523.
- [16] C.S. Park, N.L. Müller, S.A. Worthy, J.S. Kim, N. Awadh, M. Fitzgerald, Airway obstruction in asthmatic and healthy individuals: inspiratory and expiratory thin-section CT findings, *Radiology* 203 (2) (1997) 361–367.
- [17] Global Initiative for Asthma (GINA), Global Strategy for Asthma Management and Prevention, GINA 2012 update. Available from: <http://www.ginasthma.org/> (accessed 11.12.12).
- [18] E.Y. Lee, D.A. Tracy, M.D. Bastos, A.M. Casey, D. Zurakowski, P.M. Boiselle, Expiratory volumetric MDCT evaluation of air trapping in pediatric patient with and without tracheomalacia, *Am. J. Roentgenol.* 194 (5) (2010) 1210–1215.
- [19] J. Zhang, I. Hasegawa, H. Hatabu, D. Feller-Kopman, P.M. Boiselle, Frequency and severity of air trapping at dynamic expiratory CT in patients with tracheobronchomalacia, *Am. J. Roentgenol.* 182 (1) (2004) 81–85.
- [20] S. Yilmaz, A. Ekici, M. Ekici, H. Keles, High-resolution computed tomography findings in elderly patients with asthma, *Eur. J. Radiol.* 59 (2) (2006) 238–243.
- [21] S.D. Murgu, H.G. Colt, Tracheobronchomalacia and excessive dynamic airway collapse, *Respirology* 11 (4) (2006) 388–406.
- [22] C.S. Farah, C.M. Salome, Asthma and obesity: a known association but unknown mechanism, *Respirology* 17 (3) (2012) 412–421.
- [23] D.A. Beuther, S.T. Weiss, E.R. Sutherland, Obesity and asthma, *Am. J. Respir. Crit. Care Med.* 174 (2) (2006) 112–119.
- [24] WHO Expert Consultation, Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies, *Lancet* 363 (9403) (2004) 157–163.
- [25] C. Beigelman-Aubry, A. Capderou, P.A. Grenier, C. Straus, M.H. Becquemin, T. Similowski, et al., Mild intermittent asthma: CT assessment of bronchial cross-sectional area and lung attenuation at controlled lung volume, *Radiology* 223 (1) (2002) 181–187.
- [26] S. Matsuoka, Y. Kurihara, K. Yagihashi, M. Hoshino, Y. Nakajima, Airway dimensions at inspiratory and expiratory multisession CT in chronic obstructive pulmonary disease: correlation with airflow limitation, *Radiology* 248 (3) (2008) 1042–1049.
- [27] D. Litmanovich, C.R. O'Donnell, A.A. Bankier, A. Ernst, M.E. Millett, S.H. Loring, et al., Bronchial collapsibility at forced expiration in healthy volunteers: assessment with multidetector CT, *Radiology* 257 (2) (2010) 560–567.
- [28] H. Inoue, A. Niimi, T. Takeda, H. Matsumoto, I. Ito, H. Matsuoka, et al., Pathophysiological characteristics of asthma in the elderly: a comprehensive study, *Ann. Allergy Asthma Immunol.* 113 (5) (2014) 527–533.
- [29] R.H. Brown, Obesity and asthma: what we've got here is failure to communicate, *Am. J. Respir. Crit. Care Med.* 189 (12) (2014) i–ii.
- [30] A. Al-Alwan, J.H.T. Bates, D.G. Chapman, D.A. Kaminsky, M.J. DeSarno, C.G. Irvin, et al., The nonallergic asthma of obesity. A matter of distal lung compliance, *Am. J. Respir. Crit. Care Med.* 189 (12) (2014) 1494–1502.