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The Use of Endobronchial Ultrasonography in Assessment of Bronchial Wall Remodeling in Patients With Asthma

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Background: Endobronchial ultrasound (EBUS) is a new technique that enables the assessment of bronchial wall layers. The aim of the study was to verify the utility of EBUS for the assessment of bronchial wall remodeling in patients with asthma.

Methods: In 35 patients with asthma and 23 control subjects, high-resolution CT (HRCT) scanning and EBUS were used to measure bronchial wall thickness in the 10th segment of the right lung. With a radial 20-MHz probe, EBUS identified the 5-laminar structure of the bronchial wall. Layer 1 (L_1) and layer 2 (L_2) were analyzed separately, and layers 3 through 5 (L_{3-5}), which corresponded to cartilage, were analyzed jointly. Digitalized EBUS images were used for the quantitative assessment of bronchial wall thickness and the wall area (WA) of the layers. Finally, bronchial biopsy specimens were taken for measuring the thickness of the reticular basement membrane (RBM). The thickness and WA of the bronchial wall layers, which were assessed using EBUS, were correlated with FEV_1 and RBM.

Results: There was no significant difference in the measurements of total bronchial wall thickness using EBUS and HRCT scanning. The thickness and WA of the bronchial wall and its layers were significantly greater in patients with asthma than in the control subjects. A negative correlation among the thicknesses of L_1 , L_2 , and L_{3-5} and FEV_1 , and a positive correlation with RBM were observed only in the patients with asthma.

Conclusions: EBUS allows precise measurement of the thickness and WA of bronchial wall layers. The correlation of these parameters with asthma severity suggests implementation of EBUS in the assessment of bronchial wall remodeling in patients with asthma.

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Abbreviations: EBUS = endobronchial ultrasound; HRCT = high-resolution CT; L_1 = layer 1; L_2 = layer 2; L_{3-5} = layers 3 to 5; RBM = reticular basement membrane; T/D = thickness/diameter ratio; WA = wall area

In patients with bronchial asthma, a chronic inflammatory process initiates bronchial hyperresponsiveness and leads to characteristic structural changes that cause irreversible changes in the bronchial wall structure, which is referred to as *airway remodeling*. So far, two methods have been used to assess this phenomenon, and each has its drawbacks. First, a histologic examination of bronchial biopsy specimens enables the most precise (*ie*, morphologic) assessment of the remodeling of the bronchial wall and its particular layers, but it requires an invasive bronchial biopsy during bronchoscopy. Second, high-resolution CT (HRCT)

scanning allows for assessment of the total thickness of the bronchial wall, but it cannot discriminate between its layers and involves exposing patients to radiation.

A promising method for assessing airway remodeling is endobronchial ultrasound (EBUS). Most authors^{1,2} agree that EBUS makes it possible to distinguish three to five layers of the bronchial wall. The trachea and cartilaginous bronchi exhibit a five-layer structure, whereas noncartilaginous membranous parts of the airways represent a three-layer structure. The opportunity for precise imaging of the bronchial wall as well as for

discriminating its particular layers with EBUS inspired us to attempt to assess bronchial wall remodeling in asthma patients.

MATERIALS AND METHODS

Patients

Thirty-five patients with bronchial asthma and 23 control subjects with clinical indications for bronchoscopy were enrolled in the study. The diagnosis of asthma was established according to Global Initiative for Asthma guidelines. Sixteen patients had mild asthma, 9 patients had moderate asthma, and the remaining 10 patients had severe asthma. In the control group, bronchofiberscopy was performed to diagnosis hemoptysis and persistent cough or to exclude malignancy. The characteristics of the patients studied are presented in Tables 1 and 2. The study and control groups were comparable in age and gender but not in FEV₁.

Study Design

The study was classified as a prospective, controlled trial. Its protocol was approved by the Bioethical Committee of Jagiellonian University (Krakow, Poland). Informed consent was obtained from all patients.

In all patients, spirometry (Jaeger MasterLab; Jaeger-Toennies GmbH; Höchberg, Germany) was performed before and after the administration of a short-acting β_2 -agonist. Next, an HRCT scan was performed, which assessed total bronchial wall thickness in the posterior basal segment (B¹⁰), and bronchoscopy with EBUS was carried out. The bronchial wall thickness in B¹⁰ was measured through the assessment of its layers. Bronchial biopsy specimens were obtained from the carina between B⁹ and B¹⁰ for histologic examination in order to assess reticular basement membrane (RBM) thickness.

HRCT scanning was carried out with a spiral scanner (HeliCAT Twin Flash scanner; Elscint; Haifa, Israel), using a thin-section axial technique (1-mm slice thickness) and a high-spatial-frequency reconstruction algorithm. The whole thorax was scanned with the patient in the supine position at full inspiration at 10-mm intervals. The bronchial wall thickness was assessed at segment 10 of the right lung. The images were viewed at a window level of -450 Hounsfield units and a window width of 1,500 Hounsfield units. Luminal and total diameters of the bronchi were measured with a digital caliper. Bronchial wall thickness (expressed in millimeters) was calculated from the following equation:

$$T = (D - L)/2$$

where T is bronchial wall thickness, D is the total diameter of the bronchi, and L is the luminal diameter of the bronchi. The analysis was made only on the bronchi visible in cross section, when the ratio of the diameter of the long axis to the short axis was < 1.2. Three measurements of total bronchial wall thickness were performed with HRCT scanning in each patient. The mean value of the three measurements was used for the calculations.

Two radiologists were involved in HRCT scan measurements and were blinded with respect to study group. Bronchofiberscopy was carried out under local anesthesia (lidocaine, 2%), and mild sedation with fentanyl (0.05 to 0.1 mg IV) and midazolam (2.5 to 5 mg IV).

Ultrasonography was performed with a bronchofiberscope (BFIT160; Olympus; Tokyo, Japan), with a 20-MHz ultrasonographic probe and special processor (EU-M30S; Olympus). The probe was positioned in the lumen of segment 10 of the right lung (B¹⁰). The parameters were set in such a way as to enable optimal imaging of the bronchial wall. Any difficulties with imaging occurred mainly in the vicinity of the assessed bronchial

Table 1—Characteristics of the Study Participants

Characteristics	Asthma Patients (n = 35)	Control Subjects (n = 23)	p Value
Sex			0.592
Female	19	10	
Male	16	13	
Age, yr			0.899
Mean $\pm$ SD	47 $\pm$ 13.5	48 $\pm$ 14.1	
Median (25th–75th percentile)	48 (37.5–58)	50 (37–61)	
FEV ₁ , % predicted			< 0.001
Mean $\pm$ SD	74.1 $\pm$ 24.2	103.6 $\pm$ 16.3	
Median (25th–75th percentile)	77.5 (52.2–90.5)	105.9 (95.3–112.6)	

Table 2—Characteristics of Patients With Asthma

Variables	Values
Inhaled corticosteroid therapy	
Yes	35
No	0
Dose, μ g/d	
Mean $\pm$ SD	982.9 $\pm$ 605.1
Median (25th–75th percentile)	1,000 (400–1,000)
Oral corticosteroid therapy	
Yes	7
No	28
Long-acting β_2 -agonist therapy	
Yes	33
No	2
Methylxanthine therapy	
Yes	11
No	24
Skin prick test results, No.	
Positive	12
Negative	23

Values are given as No., unless otherwise indicated. The dose of any other inhaled corticosteroids was converted to the equivalent dose of budesonide.

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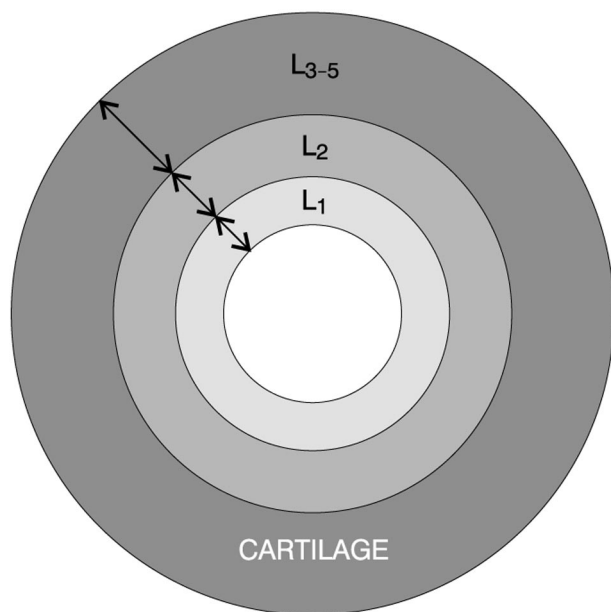


FIGURE 1. Schema of measurements of the thickness of bronchial wall layers and its WA in EBUS.

wall to the transducer and the necessity of visualizing its laminar structure. To optimize the method, we chose the tested range (1 cm), gain (0), and sensitivity time control to achieve a precise and repeatable ultrasound image of five layers of the bronchial wall. Although it was possible to discriminate all five layers in the assessment of asthma remodeling, the inner layers (layer 1 [L₁] and layer 2 [L₂]) were analyzed separately, and the outer layers (layers 3 to 5 [L₃₋₅]) that corresponded to cartilage were analyzed jointly. To enhance the precision of the remodeling assessment in EBUS, we used the following two parameters: the direct mea-

surement of the thickness of particular layers of the bronchial wall; and the area of the cross section of these layers (*ie*, the wall area [WA]) [Fig 1].

Images for calculations were saved as bitmaps and imported for further analysis into an image-editing program (Photoshop; Adobe Systems Inc; San Jose, CA). From a digital sequence of frames recorded during bronchofiberscopy, two independent radiologists chose five frames that best visualized the laminar structure of the bronchial wall. Selected images were magnified four to eight times, and the points were marked to represent the margins of particular layers of the bronchial wall. An image-magnifying option allowed a subpixel precision of the wall thickness measurements. The points were marked, and measurements were performed manually (Fig 2). Five measurements of each layer were performed, the mean value of which was treated as a final result. Two radiologists were involved in EBUS measurements, and the mean value of their measurements was used for further calculation.

Measurement of Bronchial Wall Layers WA

The measurements of the WA were carried out with feature extraction software, which was especially prepared for this study. After importing the image, a section of the circle was chosen for the analysis. The section was defined by the indication of the center and the position of its arms. The position of the investigated bronchial layer then was calculated by means of a manual measurement of the polygon on the digital image. The polygon area was calculated for the selected central angle φ , using the following Gauss equation:

$$D_{\varphi} = \frac{1}{2} \cdot \sum_{i=1}^n (x_i y_{i+1} - x_{i+1} y_i)$$

where D_{φ} is the area of layer section (selected polygon), (x_i, y_i) ; $i = 1 \dots n$ is the coordinates measured on the digital image [$(x_{n+1}, y_{n+1}) = (x_1, y_1)$], and n is the number of polygon bend points.

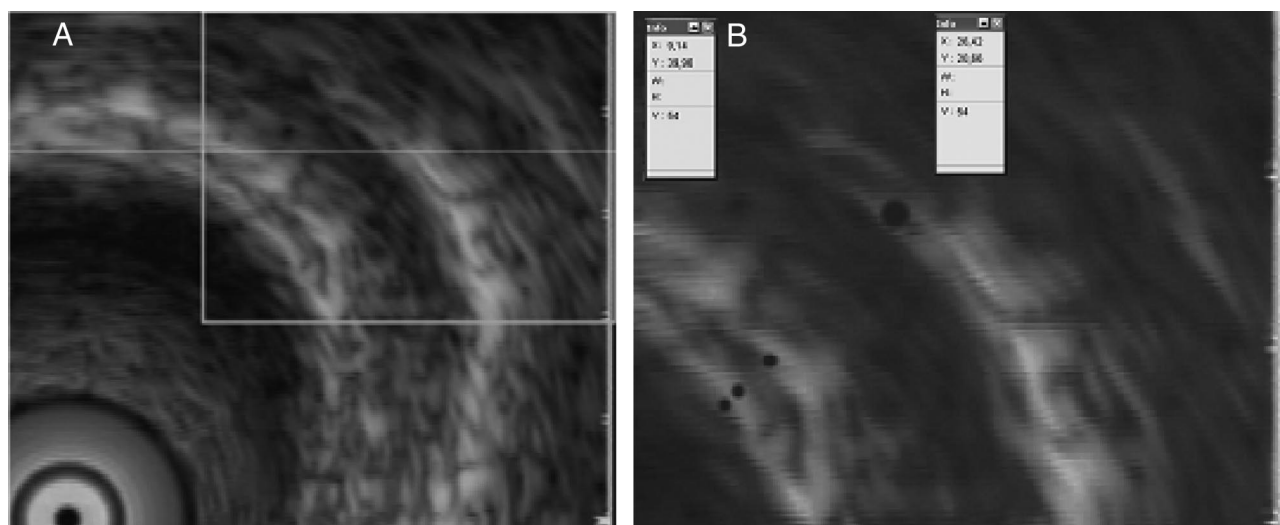


FIGURE 2. Measurements of the thickness of bronchial wall layers. A: a transverse sonogram obtained using a radial 20-MHz endobronchial probe identified 5-laminar structure of the bronchial wall (B¹⁰), with range of the scan = 1 cm; gain = 0; and near-neutral position sensitivity time control (original $\times 4$). B: borders of the bronchial wall layers are marked manually by black dots (original $\times 8$). Thickness of the layers was calculated through display-screen coordinates.

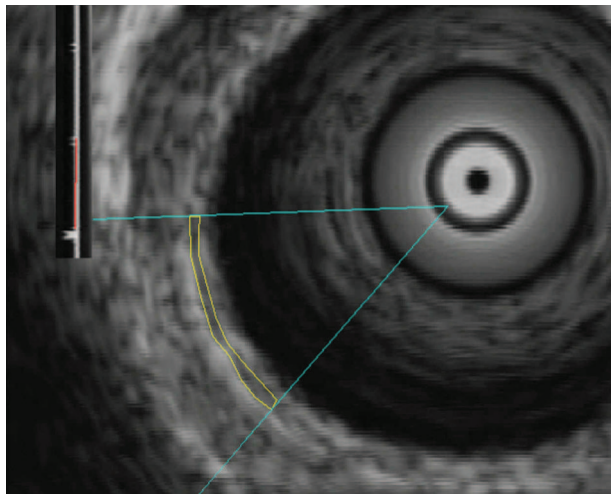


FIGURE 3. Measurement of the WA of L_2 . The analyzed area was manually defined (yellow line) in the section of the circle (green arms defined the angle), and using a semiautomatic method (feature extraction software), the area of the second layer was calculated.

The area of the whole layer ($\varphi = 2\pi$) was calculated from the following equation:

$$\text{Area} = \frac{2\pi}{\varphi} D_\varphi$$

where φ is the angle defined by the section. The measurement of the WA of the second layer is shown in Figure 3.

Histologic Examination

The tissue was fixed in 10% buffered formalin and embedded in paraffin. The 2- μm sections were prepared and stained using the periodic acid-Schiff method. The thickness of the basement membrane was measured with an imaging system (AnalySIS imaging system; Soft Imaging System GmbH; Münster, Germany) using a special image acquisition card (GraBIT PCI; Soft Imaging System GmbH). The software ran under the control of a commercial operating system (Windows XP; Microsoft Corp; Redmond, WA) and consisted of image analysis software (AnalySIS 3.2 pro; Soft Imaging System GmbH) with a custom-built application written in Imaging C language by one of the authors (K.O.). The images were acquired all along the available basement membrane, and the thickness was measured with an arbitrary-distance software tool. For each patient, at least 30 individual measurements were performed. RBM measurements were performed at intervals of 9.5 μm .

Statistical Analysis

All calculations were carried out with a statistical software package (Statistica; Statsoft; Tulsa, OK). Summary statistics were expressed as the mean (SD), or median (25th and 75th percentiles). The Bland-Altman plot was used to analyze the agreement between HRCT scan measurements and EBUS measurements, and the repeatability of measurements performed by the two independent radiologists.³ The Student t test with separate estimation of variances was used for preliminary group comparison. The general linear model for response variables, including qualitative and quantitative variables and their interactions, also

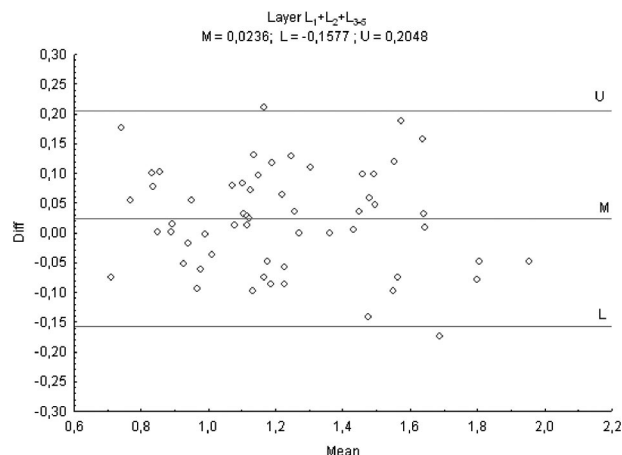


FIGURE 4. The analysis of repeatability of the measurements performed by two independent radiologists with regard to total bronchial wall thickness and its particular layers did not show any significant discrepancies (L_1 , $p = 0.6928$; L_2 , $p = 0.4989$; L_{3-5} , $p = 0.2842$; $L_1 + L_2 + L_{3-5}$, $p = 0.2697$).

was used. The correlations between variables were estimated with the Spearman rank order correlation. The level of significance was set at $p \leq 0.05$.

RESULTS

Bronchoscopy with EBUS was performed in 62 patients. In 4 patients, we did not obtain an ultrasonographic image that allowed assessment of the bronchial wall, so 58 patients were included in the final analysis. No complications were observed.

EBUS enabled us to measure the total bronchial wall thickness, its particular layers, and WA. The analysis of repeatability of the measurements performed by the two independent radiologists did not show significant discrepancies (L_1 , $p = 0.6928$; L_2 , $p = 0.4989$; L_{3-5} , $p = 0.2842$; $L_1 + L_2 + L_{3-5}$, $p = 0.2697$) [Fig 4]. Additionally, the analysis of the agreement of measurements from EBUS and HRCT scanning did not show significant differences ($p = 0.1135$), although a total bronchial wall thickness assessed using EBUS was slightly greater than that assessed with HRCT scanning (Fig 5).

Our study shows significantly greater total bronchial wall thickness in patients with asthma than in control subjects ($p = 0.004$). Further, the thickness/diameter ratio (T/D) proved significantly greater in patients with asthma than in control subjects ($p = 0.011$).

The thicknesses of L_1 and L_2 were significantly higher in the patients with asthma than in the control subjects (L_1 , $p = 0.003$; L_2 , $p = 0.001$) [Fig 6]. Similarly, L_1 and L_2 WAs were significantly greater in the patients with asthma than in the control

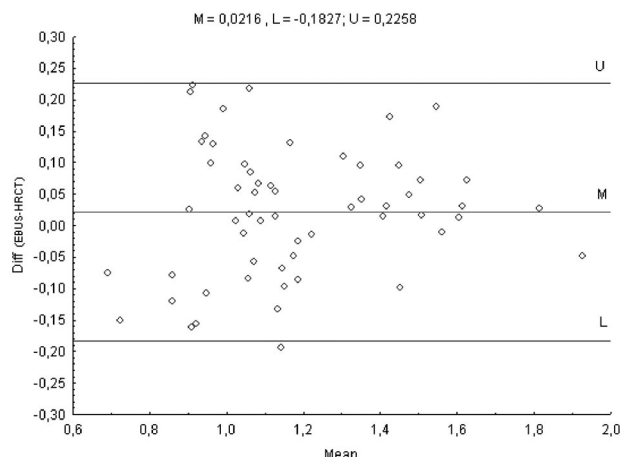


FIGURE 5. The analysis of the agreement of measurement in EBUS and HRCT did not show significant differences between these two methods ($p = 0.1135$).

subjects (L_1 , $p = 0.003$; L_2 , $p = 0.001$) [Fig 7]. RBM thickness in the patients with asthma was significantly greater than in the control subjects (6.56 and $5.13 \mu\text{m}$, respectively; $p = 0.009$). Only in patients with asthma did we manage to identify a negative correlation between layer thickness in EBUS and FEV_1 before the administration of a β_2 -agonist and a positive correlation between layer thickness in EBUS and RBM (Fig 8, 9).

DISCUSSION

Since EBUS was introduced in the 1990s, it has been continuously investigated for new clinical applications. Yamasaki et al⁴ have used EBUS to show

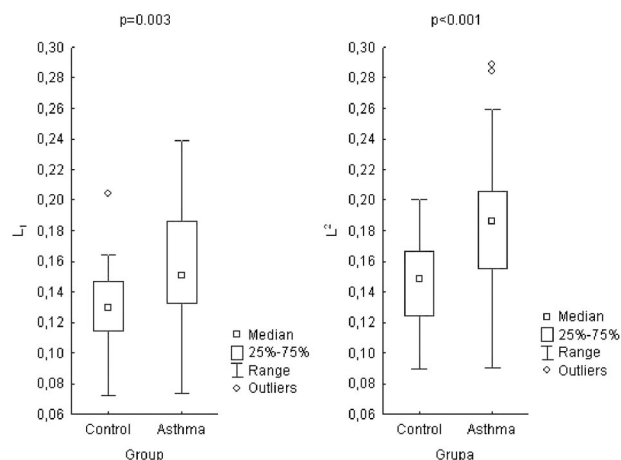


FIGURE 6. The analysis of the thickness of the bronchial wall showed that the thickness of L_1 and L_2 was significantly higher in the patients with asthma than in the control subjects (L_1 , $p = 0.003$; L_2 , $p = 0.001$).

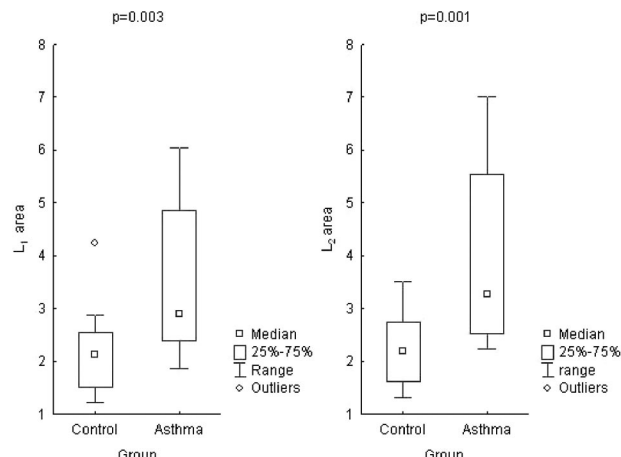


FIGURE 7. WA of L_1 and L_2 was significantly greater in the patients with asthma than in the control subjects ($p = 0.003$ and $p = 0.001$ for L_1 and L_2 , respectively).

the diminishing of subepithelial edema in patients with asthma after montelukast therapy. Miyazu et al⁵ applied this technique to the diagnosis of relapsing polychondritis with tracheobronchial malacia. Irani et al⁶ used the relative area of the layer measured with EBUS to detect lung transplant rejection or infection, and Murgu et al⁷ applied this method to assess the morphology of the bronchial wall in patients with expiratory central airway collapse.

For the first time, EBUS was proven to be useful in measuring the total thickness of the bronchial wall in sheep and in healthy human subjects by Shaw et al.⁸ They showed that the total thickness of a bronchial wall assessed with EBUS did not differ significantly from HRCT scan measurements.

In our study, we made the first attempt to apply EBUS to asthma research. We assumed that EBUS is potentially useful in the assessment of asthma remodeling. It enabled us not only to measure the total thickness of the bronchial wall in this group of patients, but also to identify the bronchial wall layers, their thicknesses, and WAs in a precise and repeatable manner. By analyzing the layers of the bronchial wall, conclusions can be drawn regarding the histologic alterations in patients with asthma.

To verify the reliability of our measurements, we tested the repeatability of EBUS findings and their consistency with those from HRCT scanning. Our analysis of the repeatability of the measurements performed by two independent radiologists did not show significant discrepancies. Additionally, the consistency of measurement analysis in EBUS and HRCT scan tests did not show significant differences between the two methods.

Our EBUS studies showed a significantly higher total bronchial wall thickness in the patients with

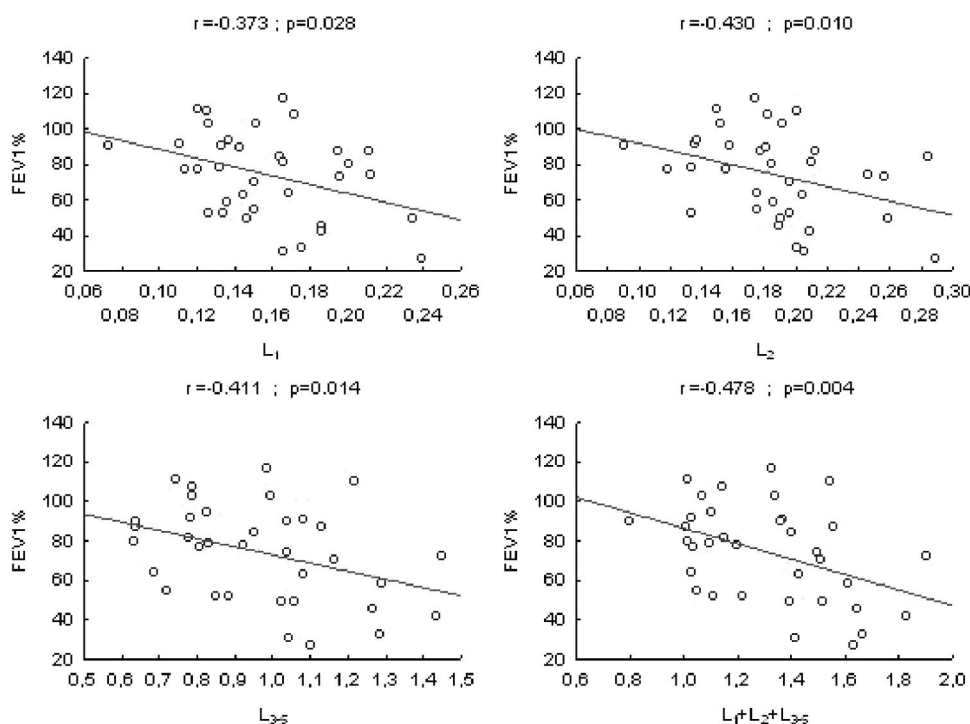


FIGURE 8. Negative correlation between layer thickness in EBUS and FEV1 in patients with asthma.

asthma than in the control subjects. This finding was supported by the results of HRCT scanning, which is a reference method in the assessment of asthma remodeling.⁹⁻¹⁶

Bronchial wall thickness in patients with asthma assessed with EBUS showed statistically significant negative correlation with FEV₁, unlike the control group. This finding is supported by those of other

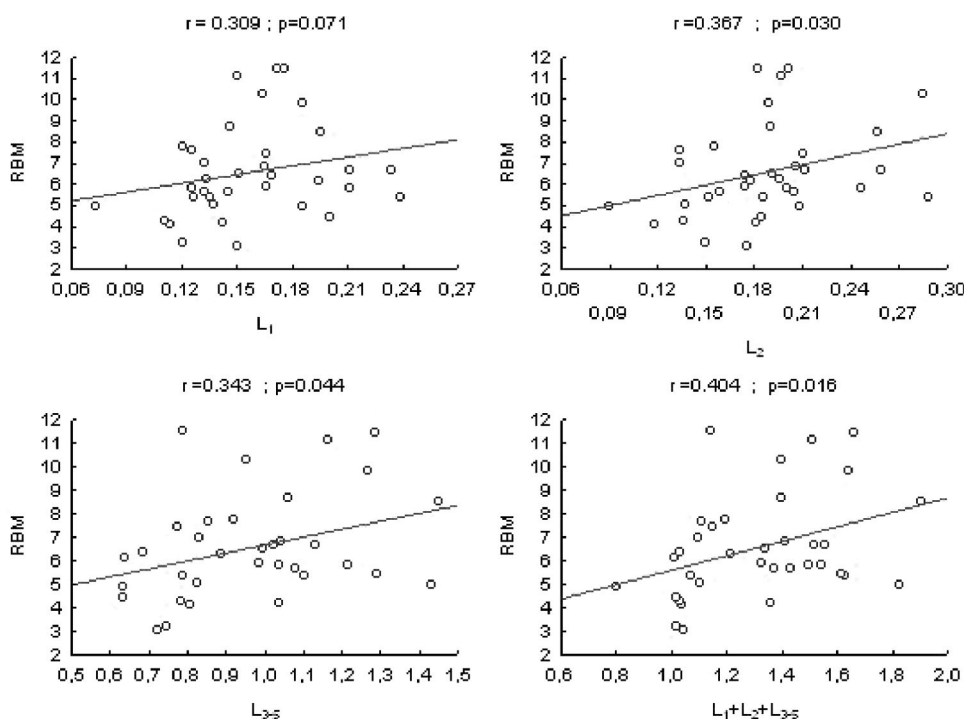


FIGURE 9. Positive correlation between layer thickness in EBUS and RBM in patients with asthma.

studies using HRCT scanning; several authors have proven the correlation between bronchial wall thickness and severity of asthma and have shown negative correlation with FEV₁ values. For example, Park et al¹⁷ showed that bronchial wall thickening occurred much more frequently in patients with asthma (44%) than in control subjects (4%). Moreover, in the patients with severe bronchial obstruction (FEV₁, < 60% predicted), the thickening was much greater than in those with mild obstruction (35%) or normal spirometry findings (38%). Paganin et al¹⁰ showed that the prevalence of thickening of the bronchial wall increases with the severity of asthma.

Our results also revealed that the T/D and WA measured by EBUS were significantly greater in the patients with asthma than in the control subjects. This finding is supported by several HRCT scan studies^{9,14,18} in which these parameters correlated with the severity of the disease, FEV₁, obstruction reversibility, and bronchial hyperresponsiveness. Moreover, Aysola et al,¹⁹ using a multidetector CT scanner, showed that the percentage of WA and the percentage of wall thickness were markedly greater in patients with severe asthma than in those with moderate and mild asthma or in control subjects. Those parameters correlated negatively with FEV₁ and positively with the response to bronchodilators, and showed a positive correlation with histologic features. Gono et al¹³ found an influence of bronchi reversibility impairment on bronchial wall thickness, showing that the T/D, the percentage of WA, and expiration/inspiration ratio describing airtrapping were significantly greater in patients with irreversible bronchial obstruction after bronchodilator administration than in patients with asthma and normal spirometry findings or in healthy control subjects. Finally, the study of Little et al¹² showed a significant and positive correlation among the percentages of WA, T/D, and severity of asthma; a negative correlation with diffusing capacity of the lung for carbon monoxide; and no relationship with FEV₁.

Not all studies, however, support these findings. Yorgancıoğlu et al²⁰ did not report any correlation among wall thickness, T/D, WA, the percentage of WA, and severity of asthma. Furthermore, Park et al,²¹ Saglani et al,²² and Marchac et al²³ did not confirm a correlation between the severity of asthma and bronchial wall thickness.

Our findings confirm that EBUS has the ability to discriminate bronchial wall layers, to measure their thickness and WA, and to assess precisely the bronchial wall remodeling in patients with asthma. Kasahara et al¹⁴ have stated that HRCT scanning allows only for measurements of total bronchial wall thickness and does not assess which bronchial wall component (*eg*, RBM or the smooth muscle) is in fact

thickened. Hence, the importance of EBUS, which allows us to overcome these difficulties. Our studies showed for the first time that the thicknesses of L₁ and L₂ (*ie*, the layers responsible for remodeling, and consisting of mucosa, the submucosal layer, and smooth muscle) are significantly higher in the patients with asthma than in the control subjects. Moreover, the thickness of these layers shows a statistically significant negative correlation with FEV₁, which implies that there is a relationship to the severity of asthma. The thickness of L₃₋₅, corresponding to cartilage, showed negative correlations with FEV₁ solely in the patients with asthma. Greater bronchial wall thickness in patients with asthma was accompanied by a significantly greater WA in all layers than that in control subjects.

In the patients with asthma, a positive correlation was shown between total bronchial wall thickness and its particular layers and RBM (for L₁, *p* = 0.079 [close to the level of significance]). In the control group, no correlation was identified. Such a trend was supported in the studies of Bourdin et al²⁴ and Kasahara et al.¹⁴ In the study of Chetta et al,²⁵ the subepithelial layer thickness in patients with severe asthma was significantly different from that in patients with mild or moderate asthma. However, some findings have been published^{22,26} that do not support these observations. Payne et al²⁷ did not observe a correlation between RBM and the severity of asthma either.

CONCLUSIONS

Besides the methods used to date, including HRCT scans and bronchial biopsies, EBUS may become a new technique for assessing asthma remodeling. In this preliminary study, EBUS was used in asthma research for the first time. Our results show greater thickness of the whole bronchial wall and its particular layers, which correlates positively with RBM and negatively with FEV₁, and indicates the relationship between these parameters and asthma severity. Thus, our findings suggest the possibility of using EBUS in the assessment of bronchial wall remodeling. It seems that in the future EBUS may be used to evaluate the effectiveness of pharmacologic and nonpharmacologic methods (*eg*, bronchial thermoplasty) of asthma treatment.

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and Szczeklik were responsible for analysis and interpretation of the data, manuscript preparation, and final approval of the article.

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The Use of Endobronchial Ultrasonography in Assessment of Bronchial Wall Remodeling in Patients With Asthma

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