INTRODUCTION

Airway remodeling in obstructive lung diseases consists of several structural changes like changes in bronchial epithelium, bronchial glands hypertrophy, smooth muscle hyperplasia and hypertrophy. Those changes are related to eosinophilic airway inflammation (1) and the inflammation launched by cigarette smoke (2). Airway inflammation and remodeling can be assessed using invasive methods like bronchoalveolar lavage fluid (3) or bronchial biopsies (4) and non-invasive ways like induced sputum (3, 5) or CT imaging. There is evidence that high resolution computed tomography (HRCT) is useful in imaging and evaluation of airway wall remodeling and morphological changes in the lung parenchyma in patients with asthma and chronic obstructive pulmonary disease (COPD) (6-9).

There is not enough data on the relation between airway inflammation or remodeling and lung function. There are some publication indicating, for example, the relationship between serum matrix metalloproteinase-9 concentration and airway obstruction (10) or macrophage surface markers in induced sputum and airflow limitation (5). On the other hand, there is growing evidence that airway inflammation and remodeling are related to genetic factors (11-13).

As it is suspected that airway remodeling leads to irreversible airway obstruction or is the main cause of the severe course of the lung obstructive diseases, there is need to search for direct relations between airway remodeling and lung function. Airway remodeling leads to bronchial wall thickening what can be assessed by HRCT (14-16). Therefore, the aim of the present study was to compare radiological features of airway remodeling in asthma and chronic obstructive pulmonary disease (COPD) patients and to assess the correlations between airway wall thickness as well as airway luminal diameter and lung function in asthma and COPD.

MATERIAL AND METHODS

The study was a part of a research project approved by the Bioethics Committee of the Medical University of Warsaw (No.
Inhaled salbutamol (400 µg via a spacer) was administered directly before HRCT scanning to achieve maximal bronchodilation during the procedure. In all patients thorax HRCT was performed with 16-row CT (Lightspeed 16 General Electric, USA), without intravenous contrast administration. The CT image data were reconstructed with a high spatial frequency algorithm and following parameters were used: collimation - 1.25 mm, current – 140 kV, 250 mA, matrix size 512 x 512. The CT image data were enlarged (magnification x 10). Cross-sections of bronchi with external diameter range 1–5 mm were selected. This was done in each patient. There was no significant difference in the airway wall thickness parameters between the studied groups (6, 22).

RESULTS

HRCT airway measurements

The mean number of airways assessed in each patient was 28±5 (25±6 in the asthma group and 29±6 in the COPD group). At each lung level (of the left and right lung) 3±1 airways were measured in each patient. There was no significant difference in the airway wall thickness parameters between the studied groups (Table 2).

Lung function tests in asthma and COPD patients

Table 3 presents the comparison of the results of lung function tests in asthma and COPD. Since the chest HRCT was performed after salbutamol inhalation, only the post-bronchodilator lung function parameters were taken into consideration in the analysis of the relations between airway dimensions and lung function.

Table 1. Demographic characteristics of asthma and COPD patients.

<table>
<thead>
<tr>
<th></th>
<th>Asthma</th>
<th>COPD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>4/6</td>
<td>7/5</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>37 ±13</td>
<td>57 ±9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24 ±3</td>
<td>26 ±4</td>
<td>NS</td>
</tr>
<tr>
<td>Severity of the disease: mild n (%)/moderate n (%)</td>
<td>5(50)/5(50)</td>
<td>7(58)/5(42)</td>
<td>NS</td>
</tr>
<tr>
<td>Onset of symptoms (age, yr)</td>
<td>18 ±19</td>
<td>53 ±10</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Duration of symptoms (yr)</td>
<td>17 ±13</td>
<td>12 ±4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ateopy n (%)</td>
<td>7 (70)</td>
<td>2 (16)</td>
<td>NS</td>
</tr>
<tr>
<td>Allergic rhinitis n (%)</td>
<td>4 (40)</td>
<td>0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pack-years</td>
<td>5 ±12</td>
<td>38 ±14</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Never smokers/past smokers/ current smokers n (%)</td>
<td>6(60)/3(30)/0(10)</td>
<td>0(54)/2(58)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Table 2. Comparison of airway dimensions assessed in HRCT in asthma and COPD patients.

<table>
<thead>
<tr>
<th></th>
<th>Asthma (n=10)</th>
<th>COPD (n=12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>D (mm) external diameter</td>
<td>3.0 ±0.7</td>
<td>2.7 ±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>L (mm) luminal diameter</td>
<td>1.3 ±0.4</td>
<td>1.2 ±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>WT (mm) wall thickness</td>
<td>0.8 ±0.2</td>
<td>0.7 ±0.1</td>
<td>NS</td>
</tr>
<tr>
<td>BWT</td>
<td>0.3 ±0.02</td>
<td>0.3 ±0.01</td>
<td>NS</td>
</tr>
<tr>
<td>( A_{w}(\text{mm}^2) ) outer area</td>
<td>7.9 ±3.5</td>
<td>6.2 ±2.2</td>
<td>NS</td>
</tr>
<tr>
<td>( A_{l}(\text{mm}^2) ) lumen area</td>
<td>1.6 ±0.8</td>
<td>1.5 ±0.8</td>
<td>NS</td>
</tr>
<tr>
<td>( A_{w}/BWSA )</td>
<td>0.9 ±0.4</td>
<td>0.8 ±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>WA (mm²) wall area</td>
<td>6.2 ±2.8</td>
<td>4.7 ±1.4</td>
<td>NS</td>
</tr>
<tr>
<td>WA/BSA</td>
<td>3.4 ±1.7</td>
<td>2.6 ±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>WA%</td>
<td>79 ±4</td>
<td>78 ±3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are means±SD. See Material and Methods for abbreviations.

Table 3. Comparison of pulmonary function (pre- and post-bronchodilator) in asthma and COPD patients.

<table>
<thead>
<tr>
<th></th>
<th>Asthma</th>
<th>COPD</th>
<th>P (asthma vs. COPD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-bronchodilator</td>
<td>Post-bronchodilator</td>
<td>Pre-bronchodilator</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>2.6 ±1.0</td>
<td>3.0 ±1</td>
<td>2.2 ±0.8</td>
</tr>
<tr>
<td>FEV₁ (%pred)</td>
<td>75 ±19</td>
<td>89 ±18</td>
<td>72 ±19</td>
</tr>
<tr>
<td>FVC (%pred)</td>
<td>96 ±13</td>
<td>103 ±12</td>
<td>100 ±25</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>3.4 ±1.2</td>
<td>4.2 ±1.2</td>
<td>3.7 ±1.4</td>
</tr>
<tr>
<td>( V_{T} ) ( V_{T} )</td>
<td>65 ±9</td>
<td>73 ±9</td>
<td>59 ±6</td>
</tr>
<tr>
<td>TLC (L)</td>
<td>6.3 ±1.1</td>
<td>6.3 ±1.2</td>
<td>6.8 ±1.8</td>
</tr>
<tr>
<td>TLC (%pred)</td>
<td>110 ±10</td>
<td>108 ±12</td>
<td>116 ±15</td>
</tr>
<tr>
<td>Raw (cmH₂O/L/s)</td>
<td>4.7 ±4.8</td>
<td>2.4 ±1.0</td>
<td>4.2 ±1.6</td>
</tr>
<tr>
<td>DLCO ml/min/mmHg</td>
<td>--</td>
<td>26.1 ±6.9</td>
<td>--</td>
</tr>
<tr>
<td>PC_{20} (mg/ml)</td>
<td>1.15 ±2</td>
<td>--</td>
<td>10.3 ±7.6</td>
</tr>
</tbody>
</table>

Table 4. Relations between airway wall thickness or airway lumen dimension and lung function in asthma patients.

<table>
<thead>
<tr>
<th></th>
<th>WA</th>
<th>WA/BSA</th>
<th>WA%</th>
<th>WT</th>
<th>BWT</th>
<th>A_{l}</th>
<th>A_{w}/BWSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-bronchodilator RV (%pred)</td>
<td>NS</td>
<td>NS</td>
<td>( r=0.72 )</td>
<td>( P&lt;0.05 )</td>
<td>NS</td>
<td>( r=0.48 )</td>
<td>( P=0.01 )</td>
</tr>
<tr>
<td>Post-bronchodilator FEV₁ (L)</td>
<td>NS</td>
<td>NS</td>
<td>( r=0.5 )</td>
<td>( P=0.1 )</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Post-bronchodilator ( V_{T} ) (%pred)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PC_{20} (mg/ml)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

\( r \)-Spearman’s correlation coefficient. See Material and Methods for abbreviations.

Table 5. Relations between airway wall thickness or airway lumen dimension and lung function in COPD patients.

<table>
<thead>
<tr>
<th></th>
<th>WA</th>
<th>WA/BSA</th>
<th>WA%</th>
<th>WT</th>
<th>BWT</th>
<th>A_{l}</th>
<th>A_{w}/BWSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLCO ml/min/mmHg</td>
<td>NS</td>
<td>NS</td>
<td>( r=0.74 )</td>
<td>( P&lt;0.05 )</td>
<td>NS</td>
<td>( r=0.70 )</td>
<td>( P=0.05 )</td>
</tr>
<tr>
<td>DLCO % pred.</td>
<td>NS</td>
<td>NS</td>
<td>( r=0.64 )</td>
<td>( P=0.08 )</td>
<td>NS</td>
<td>( r=0.61 )</td>
<td>( P=0.1 )</td>
</tr>
<tr>
<td>Post-bronchodilator Raw (cmH₂O/L/s)</td>
<td>NS</td>
<td>NS</td>
<td>( r=0.72 )</td>
<td>( P&lt;0.05 )</td>
<td>NS</td>
<td>( r=0.91 )</td>
<td>( P&lt;0.05 )</td>
</tr>
<tr>
<td>PC_{20} (mg/ml)</td>
<td>NS</td>
<td>NS</td>
<td>( r=0.61 )</td>
<td>( P&lt;0.05 )</td>
<td>NS</td>
<td>( r=0.72 )</td>
<td>( P&lt;0.05 )</td>
</tr>
<tr>
<td>Pack-years</td>
<td>( r=0.68 )</td>
<td>( P&lt;0.05 )</td>
<td>( r=0.82 )</td>
<td>( P&lt;0.05 )</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

\( r \)-Spearman’s correlation coefficient. See Material and Methods for abbreviations.

The relationship between airway dimensions and lung function in asthma patients

There was no relationship between airway wall thickness (WA% and BWT) and patients’ age or duration of symptoms. There was no correlation between airway dimensions and FEV₁% pred or FVC% pred (Table 4). Interestingly, there was a positive correlation noted between WA% and BWT and RV% pred (\( r=0.72 \); \( P<0.05 \) and \( r=0.72 \); \( P=0.05 \), respectively). A negative correlation was observed between the lumen area \( A_{l} \).
The measurements after bronchodilator inhalation. A similar study 
Therefore, to assess less reversible or irreversible airway 
obstruction related to airway smooth muscle constriction.
when measurements were undertaken after salbutamol inhalation.
comparision with healthy subjects, but there was no difference
(23) found that lumen area is smaller in asthma patients in 
Comparison of airway dimensions in asthma and COPD 
important limitation of the method.
measurements during provocative challenge tests (23, 25) and
and airway wall thickness assessed by HRCT was documented (15).
On the other hand, HRCT has its limitations. It enables the 
imaging of the total enlargement of the wall area or lumen area, 
but it does not provide with any information about each layer of 
the bronchial wall. Exposure of a patient to higher doses of 
radiation, compared with conventional chest X-ray, is still an 
important limitation of the method.
Comparison of airway dimensions in asthma and COPD 
patients
Awadh et al. (6) were one of the first researchers who applied 
HRCT to assess airway wall dimensions in patients with asthma.
Not only did they show that airway walls are thickened in asthma, 
but they also found a relationship between the severity of the 
disease and airway wall thickness. Their observations were 
confirmed by other authors (15, 26-29). Beigelman-Aubry et al. 
(23) found that lumen area is smaller in asthma patients in 
comparison with healthy subjects, but there was no difference 
when measurements were undertaken after salbutamol inhalation.
Salbutamol influences the reversible component of airway 
obstruction related to airway smooth muscle constriction. 
Therefore, to assess less reversible or irreversible airway 
structural changes associated with remodeling we performed all 
the measurements after bronchodilator inhalation. A similar study 
procedure was applied previously (15, 26). Okazawa et al. (22) 
showed that lumen area is diminished, whereas airway walls are 
thickened in asthma patients compared with healthy subjects.
Niimi et al. (27) observed that a greater thickness of the right 
apical bronchus correlates with a lower FEV1 % predicted, but 
they did not find significant differences in the lumen area in 
patients with severe compared with mild and moderate asthma 
even with healthy subjects. In the present study, there was no 
control group of healthy subjects, as the goal of the study was to 
compare airway dimensions between asthma and COPD patients.
The knowledge about airway wall thickness in COPD comes 
mainly from indirect measurements performed during autopsy 
(30) or after pulmonary tissue resection (31). It has been 
documented that in the course of the disease airway walls 
thicken and the lumen diameter is diminished (31). This was also 
noted in HRCT scans (32, 33).
We were unable to find studies directly comparing airway 
dimensions assessed in HRCT in patients with asthma and COPD. 
Harmanci et al. (7) evaluated airway remodeling in asthma and 
COPD patients using HRCT, but they focused on qualitative 
structural changes. Comparing the results of the studies by Niimi 
et al. (27) and Nakano et al. (33), it seems that the wall of the right 
apical bronchus is thicker in asthmatics when compared to COPD 
patients with the same degree of airway obstruction. The tendency, 
found in the present study, for WA%, BWT, and other airway 
thickness parameters to be insignificantly higher in the asthma 
group is in line with these observations.
The greater thickness of airway wall in asthma can be 
partially explained by histological findings. It has been shown 
that the basement membrane thickness (34), smooth muscle 
layer (30), and the number of blood vessels (35) in patients with 
asthma are greater than those in patients with COPD. Therefore, 
it is likely that airway remodeling results in a greater thickening 
of the airway wall in asthma when compared to COPD. The 
results of the present study did not directly confirm this 
hypothesis, but this may be due to a small number of patients in 
both groups studied.
Niimi et al. (27) found that in asthmatic subjects the cross 
sectional bronchial wall area was increased; however the increase 
was not accompanied by a decrease in its lumen when compared 
with healthy subjects. This finding is in contrast with that of 
Nakano et al. (33) who analyzed data from patients with COPD; 
they observed that the airway luminal area is smaller and airway 
wall thickness is greater in subjects with COPD when compared 
with healthy persons. In the present study, the airway wall 
thickness indices (WA and WT) and airway outer area (Ao) were 
greater in the asthmatic subjects when compared with patients 
with COPD. It is not clear if WA and WT are good parameters for 
the comparative analysis of airway structural changes in asthma 
and COPD. However, there are publications in which such 
comparisons are performed (27). As the values of wall area and 
airway lumen area (WA and Ao) depend on individual 
anthropometric data, these indices are often presented in relation 
to the body surface area (21, 27, 36) like it was in our study.
One should remember that features of remodeling can be 
changed by anti-inflammatory treatment like inhaled 
glucocorticosteroids (iGCS) (14), therefore patients in this study 
had not been receiving iGCS during at least 3 months preceding the 
study. Airway wall thickness observed in HRCT is related to some 
of the histological features of remodeling assessed in biopsy 
specimens (15). However, the impact of airway structural changes 
and their dimensions on lung function needs to be elucidated.
The relation between airway dimensions and lung function in 
asthma
Saglani et al. (16) and Little et al. (26) did not find any 
relation between airway wall thickness and airway obstruction, 
expressed as FEV1% predicted in asthmatics. On the other hand, 
the results of some other studies suggest that there is a correlation 
between airway wall thickening and disease severity (6, 27).
The present study results did not confirm the correlation 
between the airway wall thickness and FEV1 % predicted. It 
should be noted, however, that airway wall remodeling is only one 
of the factors contributing to airflow limitation in asthma. Mucous 
membrane edema, inflammatory cell infiltration, increased mucus 
secretion and smooth muscle constriction may influence airflow.
limitation. On the other hand, many genetic and environmental factors can influence spirometric results and airflow limitation (37-39). The impact of smooth muscle constriction was minimized by salbutamol inhalation prior to the HRCT procedure; however, the other aforementioned components of airflow obstruction could have influenced our results.

Boulet et al. (40) observed that airway hyperresponsiveness and wall thickening were related to each other in a group of asthma patients with persistent obstruction, but they did not find such a correlation in the group without post-bronchodilator airflow obstruction. In the present study, we did not note any relation between bronchial hyperresponsiveness and airway wall thickness assessed by HRCT. Our results are similar to those obtained in other studies (26, 41).

The correlation between residual volume and airway wall thickness as well as lumen area seems to be a very interesting finding. This may suggest that airway wall thickening results in air trapping in patients with asthma. This is consistent with results of some other studies (8, 28).

The relation between airway dimensions and lung function in COPD

In the present study, we found no relationship between airway wall thickening and spirometric parameters in COPD patients. However, we observed that patients with a thicker airway wall (higher BWT and WA%) had a lower PC20 value and higher airway resistance. Nakano et al. (42) evaluated the dimensions of the right apical bronchus in a group of 114 smokers and found a correlation between WA% and FEV1 % pred, FVC % pred, and the RV/TLC ratio. This suggests a relation between airway wall thickness and airway obstruction. In another study, the same authors showed that WA% in the HRCT of the proximal airways correlates with WA% assessed in biopsy specimens. Similarly, Tiddens et al. (43) observed that proximal airway wall thickening correlates with obstruction and inflammatory features found in the distal bronchi. The authors suggest that in the course of COPD, a similar inflammatory process and a similar degree of airway remodeling are present along the whole bronchial tree, regardless of the airway caliber. We may, therefore, assume that airway wall thickening of larger airways observed in HRCT indicates a similar process in small airways.

The results of the present study suggest that in COPD, greater WA% and BWT values are associated with a lower lung diffusion capacity. We might speculate that airway remodeling in COPD is accompanied by structural changes in the lung parenchyma, which impairs DLCO. Nakano et al. (33) defined two groups of COPD patients according to the type of remodeling (airway or lung tissue remodeling) predominating in HRCT. Lung tissue remodeling (emphysema) was defined as the proportion of low attenuation areas in the lungs (LAA%). The authors found that WA% and LAA% correlated with FEV1 % predicted and FVC% predicted, but only LAA% was related to DLCO (33). In the present study, we did not perform such an analysis, as we focused on the airway rather than lung parenchyma evaluation.

One of the most significant limitations of our study was a relatively small number of patients enrolled. This had two reasons: the inclusion criteria (the patients had to be steroid-naive) and lack of consent for chest HRCT which is associated with a high dose of radiation. Therefore, our results should be treated with caution. Another limitation was the lack of a second radiologist evaluating the airway dimensions. However, it should be noted that the values of airway wall dimensions regarded as most objective (WA% and BWT) were similar to those obtained in other studies, where one (27), or two radiologists (6, 15, 33) participated.

We conclude that chest HRCT seems a valuable tool in evaluating small airway dimensions in patients with asthma and COPD. The results of our study suggest that in asthma the diminished area of the airway lumen and airway wall thickening are reflected by an increase in the indices of air trapping. In COPD patients, reduction in the airway lumen area and airway wall thickening may result in higher airway resistance and responsiveness, and it is likely that airway wall thickening is related to the degree of exposure to tobacco smoke. The lack of correlation between spirometric parameters and airway dimensions assessed in HRCT indicates that the airway wall thickness and lumen diameter are not the only factors which influence airflow limitation during forced expiration.

Conflict of interests: None declared.

REFERENCES


Received: July 27, 2009
Accepted: October 15, 2009

Author’s address: Dr. Justyna Kosciuch Department of Internal Medicine, Pneumology and Allergology, Medical University of Warsaw, Banacha 1A, 02-091 Warsaw, Poland; Phone: +48 504018822; +48 22 5992751; Fax: +48 22 5991560; E-mail: j.kosciuch@o2.pl