Bronchial wall attenuation using CT as a biomarker in asthma: comparison to morphometric parameters

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Purpose

Airway changes in asthma are considered as a continuum from inflammation to remodeling and involve the whole bronchial tree [1]. Inflammatory cells within the bronchial wall, including eosinophils, T lymphocytes and mast cells, interact with smooth muscle cells leading to remodeling [2]. This latter is closely related to a lower prognosis of the disease and includes smooth muscle hypertrophy and hyperplasia, collagen deposition to basement membrane, epithelial detachment, goblet cells hyperplasia and angiogenesis [3]. In order to distinguish between different subtypes of asthma, non-invasive biomarkers are being currently evaluated [4,5].

Computed tomography (CT) has been shown to be a powerful and reliable non-invasive tool for large airways assessment. Indeed, several studies have demonstrated that morphometric parameters such as bronchial lumen area (LA), wall area (WA) or derived ratios correlate with clinical, functional and histological changes in asthmatic subjects [6-8]. However, due to the heterogeneity and complexity of needed algorithms, such post-processing programs are not yet used in routine practice [9]. Beyond geometric measurements, CT offers the unique ability of tissue attenuation measurements. Washko and coworkers recently demonstrated the value of bronchial wall peak attenuation in patients with chronic obstructive pulmonary disease (COPD) and showed significant differences with healthy subjects [10,11]. To our knowledge, such a study has never been carried out in asthma.

Because airways geometrical and histological changes occurring in asthma are likely to influence CT bronchial wall attenuation, we sought to investigate this parameter. Our aims were thus to compare airway wall attenuation value (WAV) in patients with asthma and healthy subjects, and to correlate WAV with pulmonary function testing (PFT), bronchial morphometric parameters and immunohistologic data.
Methods and Materials

Twenty-seven patients with asthma and 15 non-smoker controls were included in this study. Non-inclusion criteria were the presence of any other pulmonary disease or occupational dust exposure, the occurrence of any acute thoracic event for at least six weeks prior to examinations, the presence of extensive bronchial calcifications on CT and a history of medication by warfarin [12].

PFT were performed using body plethysmography according to the ATS/ERS guidelines.

All CT scans were obtained using a 16-slice MDCT system. Data were obtained at full inspiration with no contrast media injection and using the following parameters: 100-120-kV tube voltage, 50-60-mA.s tube current and 0.75-mm collimation. Images were reconstructed with a smooth standard algorithm (B30f), 1-mm section thickness, 1-mm interval, 280-380-mm square field of view and 512 x 512 matrix.

Images were analyzed in a random order using Myrian software (Intrasense, Montpellier, France) by a single observer with a 5-year experience in chest CT. Apical bronchus (B1) of the upper lobes and posterobasal bronchus (B10) of the lower lobes were identified. The slice where each bronchus had minimal contact with the adjacent vessel was selected for measurements. The observer, blinded to clinical and PFT data, manually selected all pixels within the bronchial wall, then all pixels within the bronchial lumen to measure the mean WAV, WA and LA. The following morphometric indexes were also computed: WA/LA, WA/TA, and wall thickness (WT). All values were averaged over the 4 studied bronchi.

In 8 healthy subjects and 8 asthmatics, not included in the final population, WAV was measured by the same observer one month later, and by a second observer in a blinded fashion.

Bronchoscopy with systematic biopsies of the middle lobe bronchus spur was performed in patients with refractory asthma (n=11) and in patients with haemoptysis (n=2). Inflammation and remodeling components were quantified for each patient.

Intra and interobserver agreement was assessed using Bland-Altman method and analytically. Subjects' characteristics, PFT and CT results were compared using either unpaired t-test or Wilcoxon-rank test according to data distribution. Sensitivity-to-specificity relationship was analyzed for CT parameters using receiver operating characteristics (ROC) curves. Areas under the curve (AUC) were compared using t-statistics. Pearson's correlation coefficients were determined between WAV, morphometric parameters and PFT results. Spearman's correlation coefficients were calculated between WAV and histological results.
Results

Subjects’ characteristics, PFT and CT

All morphometric CT parameters except WA and WT allowed to separate asthmatics from controls.

WAV was greater in asthmatics (-322 ± 79 HU) than in controls (-463 ± 69 HU).

<table>
<thead>
<tr>
<th></th>
<th>CONTROLS</th>
<th>ASTHMATICS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.47 ± 14.63</td>
<td>51.96 ± 14.90</td>
<td>0.754</td>
</tr>
<tr>
<td>Sex-ratio (M/F)</td>
<td>10/5</td>
<td>10/17</td>
<td>0.065</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.87 ± 15.14</td>
<td>77.52 ± 16.08</td>
<td>0.946</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.80 ± 8.53</td>
<td>165.70 ± 10.27</td>
<td>0.327</td>
</tr>
<tr>
<td>TLC (%)</td>
<td>96.83 ± 14.55</td>
<td>97.46 ± 14.89</td>
<td>0.894</td>
</tr>
<tr>
<td>RV (%)</td>
<td>81.65 ± 10.80</td>
<td>112.56 ± 34.43</td>
<td>0.006 *</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>109.76 ± 13.78</td>
<td>75.21 ± 24.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>105.88 ± 15.67</td>
<td>87.46 ± 23.33</td>
<td>0.009</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>83.63 ± 9.75</td>
<td>72.03 ± 13.44</td>
<td>0.013 *</td>
</tr>
<tr>
<td>FEF 25-75% (%)</td>
<td>98.14 ± 20.01</td>
<td>51.81 ± 27.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Air SD (HU)</td>
<td>14.25 ± 2.73</td>
<td>14.34 ± 3.41</td>
<td>0.935</td>
</tr>
<tr>
<td>Pixel size (mm)</td>
<td>0.71 ± 0.04</td>
<td>0.67 ± 0.06</td>
<td>0.037 *</td>
</tr>
<tr>
<td>WAV (HU)</td>
<td>-463.24 ± 68.83</td>
<td>-321.64 ± 79.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LA (mm²)</td>
<td>18.23 ± 3.82</td>
<td>14.12 ± 4.50</td>
<td>0.005</td>
</tr>
<tr>
<td>WA (mm²)</td>
<td>28.37 ± 5.04</td>
<td>27.11 ± 4.60</td>
<td>0.417</td>
</tr>
<tr>
<td>WT (mm)</td>
<td>1.44 ± 0.13</td>
<td>1.51 ± 0.15</td>
<td>0.126</td>
</tr>
<tr>
<td>WA/LA</td>
<td>1.63 ± 0.20</td>
<td>2.16 ± 0.60</td>
<td>&lt;0.001 *</td>
</tr>
<tr>
<td>WA/TA</td>
<td>0.61 ± 0.02</td>
<td>0.67 ± 0.05</td>
<td>&lt;0.001</td>
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</tbody>
</table>
**Fig.**: Data are anthropometric characteristics, pulmonary function tests and CT results in each group. Comparisons between groups were achieved using unpaired t-test except for sex-ratio (Khi 2 test) and * (Wilcoxon rank test). TLC: total lung capacity, RV: residual volume, FEV1: forced expiratory volume in 1 second, FVC: functional vital capacity, FEF 25-75%: forced expiratory flow between 25 and 75% of FVC. SD: standard deviation, WAV: wall attenuation value, LA: lumen area, WA: wall area, WT: wall thickness, WA/TA: wall area to total area ratio.

**References:** Thoracic and Cardiovascular Imaging Unit, Hôpital Haut-Lévêque - Pessac/FR

**Fig.**: Representative thin section-CT images in a control subject (a-d) and an asthmatic (e-h). Original images (a, e) with the studied bronchus (right B1) shown by
the arrow, magnification of the bronchus of interest (b, f), delineation of the bronchial wall (c, g) and the bronchial lumen (d, h). Wall attenuation values were -491 and -250 HU for the control subject and the asthmatic, respectively.

References: Thoracic and Cardiovascular Imaging Unit, Hôpital Haut-Lévèque - Pessac/FR

Intra and inter-observer agreement of WAV measurement

Agreement across observers and over time was very good with intra-class coefficients equal to 0.95
**Fig.**: Graphs obtained for intra (a, c, e) and inter-observer (b, d, f) variability of wall attenuation value (WAV) measurements. (a, b): correlations between measurements. The diagonal dashed line corresponds to the line of equality and the solid line to the regression line. (c, d): means of measurements plotted against their difference according to Bland-Altman analysis. The solid line corresponds to the mean difference. The dashed lines correspond to the 2 standard deviations. For each standard deviation, a 95% confidence interval can be calculated (dotted lines). (e, f) Means of measurements plotted against their standard deviations.

**References:** Thoracic and Cardiovascular Imaging Unit, Hôpital Haut-Lévêque - Pessac/FR

**Diagnostic performance of CT parameters**

ROC curves of WAV, WA/LA, WA/TA and LA for diagnosing asthma are shown below. AUC was significantly greater than 0.5 for each parameter except WA and WT. The ability of WAV in predicting asthma was significantly greater than that obtained with LA, WA and WT and trended to be greater than that of WA/LA and WA/TA.
**Fig.**: Receiver operating characteristics curves for wall attenuation value (black solid line), wall area to total area ratio (grey dotted line), wall area to lumen area ratio (black dashed line) and lumen area (grey solid line) to predict patients' group.

**References:** Thoracic and Cardiovascular Imaging Unit, Hôpital Haut-Lévèque - Pessac/FR

**Correlations between PFT results and CT parameters**

Significant correlations were found between CT parameters and PFT results. WAV best correlated with FEV1 and FEF 25-75%. Pearson's correlation coefficients of WAV with each PFT parameter were always greater than those obtained for any morphometric CT parameter.
Fig.: Correlation between bronchial wall attenuation value (WAV) and (a) forced expiratory volume in 1 second (FEV1) and (b) forced expiratory flow between 25 and 75% of functional vital capacity (FEF 25%-75%). Triangles: controls, circles: asthmatics. Solid lines correspond to regression lines.

References: Thoracic and Cardiovascular Imaging Unit, Hôpital Haut-Lévêque - Pessac/FR

Correlations between WAV and immunohistologic data

WAV correlated with the infiltration of the bronchial wall by non degranulated mast cells when considering either all patients (r=0.88 ; p<0.001) or only asthmatics (r=0.87 ;
p=0.002). WAV also correlated with the muscular to subepithelial area ratio (r=0.70; p=0.007) when considering all subjects.

**Fig.** Correlation between wall attenuation value (WAV) and (a) the count of non degranulated mast cells within the bronchial wall (AA1 Total) and (b) the count of total mast cells within the muscle layer (c kit R ML). Triangles: controls, circles: asthmatics.

**References:** Thoracic and Cardiovascular Imaging Unit, Hôpital Haut-Lévèque - Pessac/FR
Conclusion

As partial volume effects with air have been shown to overestimate WA [13], they are likely to decrease the actual attenuation value of bronchial wall, yielding negative values, a result also found by others [10,11]. However, due to its arithmetic concept, WAV might be less dependent on spatial resolution than morphometric parameters are. Indeed, WAV is a mean of numeric values, while WA or WT is a sum. In other words, pixel attenuation values are averaged for WAV measurements, while pixel areas are added up for morphometric parameters.

This study demonstrates that bronchial wall attenuation is a reproducible parameter that distinguishes asthmatics from control subjects, correlates with obstructive indexes and, in a subset of our population, with some immunohistological parameters. WAV correlated with the smooth muscle to subepithelial layer area ratio, which is considered as a marker of remodeling [14]. The only cellular population correlating with WAV was mast cells, especially within the smooth muscle layer. Mast cell has been shown to be a key cell of the chronic inflammatory process leading to bronchial smooth muscle remodeling [15]. Therefore, WAV might be a biomarker of mast cell infiltration and/or subsequent remodeling.
References


