The Prediction of Small Airway Dimensions Using Computed Tomography


Chronic obstructive pulmonary disease is characterized by destruction of the lung parenchyma and/or small airway narrowing. To determine whether the dimensions of relatively large airways assessed using computed tomography (CT) reflect small airway dimensions measured histologically, we assessed these variables in nonobstructed or mild to moderately obstructed patients having lobar resection for a peripheral tumor. For both CT and histology, the square root of Aaw was plotted versus lumen perimeter (Pi) measured with both techniques were related (CT slope between the square root of Aaw and internal perimeter (Pi) measured with both techniques were related (CT slope × 0.2059 histology slope = 0.1701, R² = 0.32, p < 0.01). The mean wall area percentage measured by CT for airways with a Pi of greater than 0.75 cm predicted the mean dimensions of the small airways with an internal diameter of 1.27 mm (R² = 0.57, p < 0.01). We conclude that CT measurements of airways with a Pi of 0.75 cm or more could be used to estimate the dimensions of the small conducting airways, which are the site of airway obstruction in chronic obstructive pulmonary disease.

Keywords: bronchioles; bronchiolitis; chronic obstructive pulmonary disease; emphysema; small airways

Chronic obstructive pulmonary disease (COPD) is characterized by decreased maximal expiratory airflow, hyperinflation, and gas trapping. These physiologic abnormalities are caused by a combination of loss of lung elastic recoil and narrowing of the small airways. Emphysema is the pathologic lesion most closely associated with the loss of elasticity and increased total lung volume, whereas inflammation and fibrosis of the membranous bronchioles accompanied by mucous plugging characterize the pathologic lesions that contribute to the small airway narrowing (1–4). Together these abnormalities cause increased airway resistance and premature airway closure. Several studies have established (2, 5, 6) that the major site of airway obstruction in patients with COPD is in airways smaller than 2-mm internal diameter, and a recent histologic evaluation of a large group of cases has shown that the decline in FEV₁ in COPD is related to thickening of the walls of these small conducting airways (4). There is also evidence that the pathophysiologic pathways that lead to emphysema and to small airway narrowing are independent; individual patients may have predominantly small airway or parenchymal disease. Recently, Nakano and colleagues (7) showed that an increase in thickness of the apical segmental bronchus in the right upper lobe measured on high-resolution computed tomography (HRCT) was related to the severity of airflow obstruction and gas trapping (FEV₁, FVC, and FEV₁/FVC) in smokers who had COPD independently of the degree of emphysema measured on the same HRCT scans. Unlike the degree of emphysema, the HRCT airway dimensions were not related to the diffusing capacity. Because the important site of airway narrowing in COPD is the bronchioles, these data suggest that thickening of large airways may be a surrogate for small airway abnormalities. It is possible that the same pathophysiologic process, which results in excessive obstruction of small airways, also occurs in the larger airways (8). Although increased airway wall thickness in the larger airways may have little functional consequence, the ability to measure thickening using CT could prove to be a useful predictor of small airway pathology and may allow for phenotypic stratification of patients who have COPD into parenchymal- and airway-predominant categories. To test this hypothesis, we measured the airway dimensions of large- and intermediate-sized airways using HRCT and compared these measurements with histologic estimates of small airway remodeling in resected human lungs. Some of the results of this study have been previously reported in an abstract (9).

METHODS

This study was part of an ongoing investigation of lung structure and function (10). Twenty-two patients gave informed consent to have their lung function, computed tomography (CT) scans, and resected tissue examined in research studies using methods approved by the Providence Health Care Clinical Ethics Review Board. The subjects were consecutive patients who required pneumonectomy or lobectomy for small peripheral lung nodules; they were not selected to represent an obstructed and nonobstructed group.

Before surgery, subdivisions of lung volume, spirometry, and single-breath diffusing capacity were measured as previously described, and they conformed to American Thoracic Society standards (10–12). Immediately after resection, the lung or lobe was obtained from the operating room, inflated to a transpulmonary pressure of 20 cm H₂O, and immediately after resection, the lung or lobe was obtained from the operating room, inflated to a transpulmonary pressure of 20 cm H₂O, and positioned in either a GE CT/i or a High-Speed Advantage CT scanner (General Electric Medical Systems, Milwaukee, WI) in an orientation similar to a clinical supine CT scan. Axial images were acquired using either 1.0- or 1.5-mm collimation and were reconstructed using a high spatial frequency reconstruction algorithm.

After completion of the CT scan, the resected lung or lobe was prepared for histology as previously described (13) and detailed in the online supplement. Images of all intact membranous and cartilaginous airways cut in reasonable cross-section (long/short diameter of 3.3 or less) were captured using a digital camera at an appropriate magnification (14). The digital images of the airways were analyzed using Image
The pulmonary function of the patients is shown in Table 1. Five of the 22 subjects were nonsmokers, and 1 had smoked for only 1 year. These data show that there is a wide range in the level of obstruction, but most had only mild obstruction (Global Initiative for Obstructive Lung Disease [GOLD] classes 1 and 2) (16). Figure 1 shows the relationship between Pi and √Aaw measured by CT and histology for one patient. Examination of Figure 1 illustrates that the size (Pi) of the airways measured using CT is larger than the membranous and cartilaginous airways assessed by histologic examination, although there is some overlap. It is also apparent that the Aaw at any Pi is substantially greater as measured by CT than on histologic examination. There was a small significant difference in the slopes of √Aaw versus Pi (0.23 ± 0.03 vs. 0.28 ± 0.09, p = 0.002) measured by CT and histology, respectively. However, there was a large significant difference in the intercepts (0.15 ± 0.01 vs. 0.02 ± 0.01, p < 0.0001). There was also a significant relationship between the slopes measured using histology and CT (i.e., individuals who had a steep slope of Pi vs. √Aaw on histology also had a steep slope on CT) (CT slope = 0.2059, histology slope = 0.1701, R² = 0.32, p < 0.01; Figure 3). A weak but significant correlation was also found for the relationship between intercepts (R² = 0.13, p < 0.05).

Because we have previously shown (14) that there is an overestimation of Aaw on CT and that this overestimation is greatest in small airways, we performed an analysis restricted to the larger airways on CT. We calculated the WA% for all airways with an Pi of greater than 0.75 cm measured on CT (mean ± SD Pi = 1.036 ± 0.142 cm) and compared this value with the histologic estimate of small airway remodeling (√Aaw at a Pi = 4 mm). We chose the value of √Aaw at a Pi = 4 mm because this conforms to airways with an internal diameter of approximately 1.27 mm, which is the size of airways that has been shown to be the site of increased resistance in COPD (2). Figure 4 shows the significant relationship between the CT measured WA% of all airways with a Pi of more than 0.75 cm and the predicted √Aaw for airways with a Pi of 4 mm measured on histology (R² = 0.57, p < 0.01). This relationship was also significant when we used a CT Pi cutoff of 1 cm (R² = 0.39, p < 0.01).

**DISCUSSION**

The results of this study indicate that the airway dimensions of the large- and intermediate-sized airways, which can be accurately assessed using HRCT scanning, reflect airway dimensions in the smaller airways, which are the most important site of airway obstruction in COPD.

Two pathophysiologic processes contribute to the pathogenesis of COPD: proteolytic destruction of the lung’s connective tissue framework, which causes emphysema and loss of lung recoil and inflammatory/fibrotic narrowing of peripheral airways (4, 17, 18). Both of these processes result in similar physiologic derangements, including increased airway resistance, decreased maximal expiratory flow, hyperinflation, gas trapping, and gas exchange impairment. It is possible that different genetic susceptibility, interacting with environmental factors, favors the predominant development of one of these pathophysiologic processes in individual smokers. The work of Nakano and colleagues (7) suggested that these phenotypes can be separated by measuring the percentage of low attenuation area in the lung as a marker of emphysema and the dimensions of the apical segmental bronchus to the right upper lobe as an estimate of airway remodeling. He found that the percentage of low attenuation area and relative Aaw (WA%) independently contributed to the prediction of FEV₁, FVC, and FEV₁/FVC but that only the percentage of low attenuation area was related to diffusing capacity.

However, the apical segmental bronchus is a large cartilaginous airway, and narrowing of such airways is not thought to contribute significantly to increased airway resistance in patients who have COPD. It has been shown (2) that the major site of airway obstruction in patients who have COPD is in airways smaller than 2-mm internal diameter (Pi = < 6 mm), and this finding has been confirmed (5, 6). On the other hand, Tiddens and colleagues (8) showed that histologic estimates of cartilagi-
nous airway dimensions were related to airflow obstruction and to peripheral airway inflammatory scores. We reasoned that the airway wall remodeling and luminal narrowing might involve all levels of the tracheobronchial tree in susceptible smokers and be detectable using HRCT. Although it is the thickening and narrowing of the peripheral airways that leads to the most important functional consequences, thickening of larger airways could provide a surrogate measure of the small airway process. The results of this study support this hypothesis and extend the observations of Nakano and colleagues (7).

We have previously demonstrated that the fractional error in estimation of airway wall and lumen area increases in small airways (14, 19). This error is caused by a systematic overestimation of wall area and underestimation of Air. The reasons for the systematic error include but are not limited to the following: (1) Volume averaging: airways do not always run perpendicular to the scanning plane of the CT and even with a slice thickness of only 1 mm, angling of the airway can lead to significant error (15). (2) The mucosal folds in an air-inflated lung are filled with liquid (20) so that the potential lumen area in the folds cannot be appreciated on CT scans but is included in the determination of maximal lumen area on histologic assessment. (3) Airway smooth muscle relaxation induced by fixation after the scanning based on previously published criteria for airway selection (4, 14). The smaller ratio used for the CT analysis reflects the greater potential for overestimation of wall area using this method because of volume averaging over the 1- or 1.5-mm slice thickness. Although the use of the different ratio cutoffs could lead to slight differences in the wall areas estimated by the two methods, we do not think it is a significant source of discrepancy or would affect our major conclusions.

The overestimation of Aaw by CT is confirmed in our data, as illustrated in Figure 1; the fractional difference between √Aaw measured by CT and histology is greatest in small airways and diminishes in larger airways. Despite this overestimation, Figure 3 illustrates that there is a significant correlation between CT and histology slopes of Pi versus wall area, and we also found a weak but significant correlation of the intercepts. These results suggest that despite systematic overestimation of wall area, CT airway dimensions reflect histologic airway dimensions. Furthermore, a comparison of CT and histology using CT measurements derived only from the larger airways showed that the mean WA% in airways with a Pi of approximately 1 cm on CT was correlated with the histological estimates of wall area in airways with a Pi of 4 mm. We limited this analysis to the larger airways as the relationship between Pi and Aaw on CT is heavily influenced by the more numerous smaller airways in which Aaw is overestimated for the reasons discussed previously here. In addition, WA% for the more accurately measured airways (> 0.75 and 1.0 cm) is a useful summary value because it provides an easily understood and implemented pooling of the results from

**TABLE 1. PULMONARY FUNCTION DATA**

<table>
<thead>
<tr>
<th></th>
<th>Mean (Median)</th>
<th>Range</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>64</td>
<td>35–74</td>
<td>9</td>
</tr>
<tr>
<td>Male/female</td>
<td>11/11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 % predicted</td>
<td>83 (85)</td>
<td>55–114</td>
<td>16</td>
</tr>
<tr>
<td>FVC % predicted</td>
<td>92 (96)</td>
<td>56–122</td>
<td>17</td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>71 (74)</td>
<td>49–89</td>
<td>10</td>
</tr>
<tr>
<td>Dlco % predicted</td>
<td>76 (75)</td>
<td>43–130</td>
<td>23</td>
</tr>
<tr>
<td>Smoking pack-years</td>
<td>29 (18)</td>
<td>0–90</td>
<td>25</td>
</tr>
</tbody>
</table>

*Definition of abbreviation: Dlco = carbon monoxide diffusing capacity.*

**Figure 2. Airway measurement (14)** (also detailed in online supplement). (A) A seed point is placed in the lumen of a magnified airway, and the X-ray attenuation values are measured along 64 rays projected from the seed point. The Aaw is defined using the “full width at half maximum” principle of each ray, and the lumen and wall perimeter are measured by connecting the endpoints of the lines. (B) Manual editing of rays is used to remove rays that project beyond the airway wall into neighboring dense structures such as pulmonary arteries.

**Figure 3.** Comparison of slopes: The slope of Pi versus √Aaw on histology is plotted against the slope of √Aaw (y = 0.2059x + 0.1701, R² = 0.3206, p < 0.01).
different sized airways. We also analyzed the wall area at a specific Pi on CT and found a significant although less powerful association with the histologic estimates (data not shown).

The CT scans of the lobes and lungs were obtained after resection. This allowed precise control of the transpulmonary pressure to which the lobes were inflated and complete absence of movement artifact related to breathing or cardiac motion. In addition, the scans were obtained using a field of view of 20 cm instead of the 35–40 cm used during in vivo scans. Therefore, the voxel dimensions in this study were approximately one-fourth of the voxel size on most clinical CT scans, indicating that CT images may need to be reconstructed using a field of view of 20 cm to attain the same precision as this study.

The aim of this study was not to relate lung function to airway dimensions because the number of subjects was relatively small and their degree of airway obstruction relatively mild. Although there were trends for a relationship between histologic and CT airway dimensions and emphysema in smokers: correlation with lung function. Am J Respir Crit Care Med 2008;162:1102–1108.


