Introduction to Remodeling and Repair in Respiratory Diseases*

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This special issue of CHEST is a compilation of articles provided by the speakers at a recent meeting organized by the Lovelace Respiratory Research Institute. The meeting, which focused on “Remodeling and Repair in Respiratory Diseases,” was held at the historic La Fonda Hotel in Santa Fe, New Mexico, on October 14–17, 2001. Despite concerns about travel resulting from the terrorist acts on September 11, 2001, the meeting was attended by over 150 scientists from 12 countries.

Respiratory diseases account for one death in four in the United States. Unlike many other high-impact diseases, such as heart disease and cancer, the incidence of many respiratory diseases, such as asthma and COPD, is increasing. Environmental factors are thought to be involved in many of these diseases, but except for the obvious impact of cigarette smoking, the exact factors and their mechanisms of action are still largely unknown. Although some progress has been made in treating these disorders, therapy is largely still supportive. Little is known about the processes responsible for the remodeling involved in the physiologic changes, nor do we know much about mechanisms that could be stimulated to effect repair of the damage. This meeting focused on the structural changes and their functional consequences as they occur in ARDS, asthma, pulmonary hypertension, fibrosis, neonatal diseases, and COPD. Each session of the symposium featured invited presentations by experts in their respective fields, complemented by poster presentations contributed in response to a call for abstracts.

This meeting was the fourth in a series sponsored by Lovelace Respiratory Research Institute. The topic of the 2002 meeting was “Molecular Approaches to the Early Diagnosis and Treatment of Respiratory Diseases,” held at the same location on October 13–16, 2002. More information is available at the symposium website: www.lovelace-symposium.org.

Quantitative Assessment of Airway Remodeling Using High-Resolution CT*

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Asthma and COPD are the most prevalent of lung diseases and contribute an enormous burden of morbidity in North America and globally. In both conditions, inflammation leads to airway remodeling, which contributes to airway narrowing. To date, airway remodeling has only been assessed using histological examination of airways. However, it may now be possible to assess and quantify the extent of airway remodeling in vivo using high-resolution CT (HRCT). The aim of this article is to review the use of HRCT in the investigation of airway remodeling. A number of investigators have reported techniques to make measurements of airway dimensions using CT and an increasing number of quantitative methods are being developed. Using these techniques, airway dimensions have been examined in patients with asthma and COPD. In patients with asthma, the airway wall area was increased without a decrease in luminal area, whereas in patients with COPD, the airway luminal area was decreased and airway wall area was increased. The different pattern of remodeling may reflect fundamental differences in the inflammatory processes in asthma and COPD and could influence the reversibility of the narrowing. It has also been shown that, by quantifying both the extent of emphysema and of airway remodeling, CT is useful in differentiating COPD patients who have primarily parenchymal disease from those who have primarily airway pathology. With additional advances in technology, it is likely that quantitative assessment of airway wall dimensions will ultimately provide a valuable tool for the study of airway disease.

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Key words: airway remodeling; asthma; COPD; computed tomography

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Asthma and COPD are the most prevalent of lung diseases, and they contribute an enormous burden of morbidity in North America and globally.\textsuperscript{1,2} Schema outlining the pathophysiologic mechanisms underlying asthma and COPD are shown in Figures 1 and 2. In both disorders, environmental factors such as allergens, viruses, and bacteria as well as personal, occupational, and atmospheric pollution cause an exaggerated immune/inflammatory response in genetically susceptible individuals. The inflammatory response leads to airway remodeling, which contributes to airway narrowing. There is also accumulating evidence that airway remodeling plays a role in the pathogenesis of other airway diseases such as bronchiectasis, cystic fibrosis, and bronchiolitis.\textsuperscript{3} Although airway remodeling has not been precisely defined, we propose the following description: (a) Airway remodeling is characterized by changes in the composition, quantity, and organization of the cellular and molecular constituents of the airway wall. (b) Remodeling is a consequence of chronic injury and repair. (c) Remodeling may be reversible or irreversible. (d) Remodeling leads to functional changes.

To date, airway remodeling has been assessed using only histologic examination of Airways. However, with the refinement of the precision and resolution of high-resolution CT (HRCT), it may now be possible to assess and quantify the extent of airway remodeling in vivo.\textsuperscript{4} Technical improvements have increased the spatial resolution of HRCT, making it theoretically possible to examine small airways. However, qualitative and semiquantitative measures of airway wall remodeling are open to subjective bias and have been shown to be less accurate.\textsuperscript{5} An increasing number of quantitative methods are being developed, and it is these studies we will review herein because of the enormous potential provided by the digital data on which this imaging modality is based.

A number of investigators have reported techniques to make measurements of airway dimensions using CT. In most of these studies a visual assessment was used.\textsuperscript{6–12} Visual assessment is time-consuming and, as mentioned above, results in the potential for observer bias and considerable intra- or interobserver error. Because CT data are based on the variable absorption of radiographs by tissue, which is measured by Hounsfield units (HU), a more direct and objective method to measure airway dimensions is preferable. There are several quantitative methods reported that used CT data directly. McNitt-Gray and coworkers\textsuperscript{13} tested an analysis method in which a threshold number was used to detect the airway luminal area (Ai); all pixels with values below this threshold were designated as lumen. They found that a threshold value of \(-500\) HU yielded the most accurate measurements of the lumen of a bronchial phantom. This threshold is consistent with the findings of other studies.\textsuperscript{12,14} Wood and coworkers\textsuperscript{15} made quantitative measurements of airway wall and lumen areas from spiral CT data. The first step in their analysis was to convert the asymmetric CT voxels into cubic dimensions (isotropic voxels). The voxels were converted to approximately \(0.4 \times 0.4 \times 0.4\)-mm voxels by interpolation in the longitudinal axis. This manipulation allowed the images to be reconstructed in any orientation. They then defined the central axis of the airway and reconstructed the airway lumen in a plane perpendicular to this axis. This analysis technique overcomes the major limitation to the use of HRCT in quantitative analysis, which is that accurate or true \(A_i\) and airway wall area (Aaw) can be measured only from airways that are oriented approximately perpendicular to the plane of scanning.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Pathophysiologic schema for the development of asthma.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Pathophysiologic schema for the development of COPD.}
\end{figure}

\textbf{Abbreviations:} \ Aaw = airway wall area; \ Ai = airway luminal area; \ HRCT = high-resolution CT; \ HU = Hounsfield units; \ LA/A\% = low attenuation area/total lung area \(\times 100\); \ WA/A\% = Aaw/(Aaw + Ai) \(\times 100\)
Amirav and colleagues\textsuperscript{16} developed an operator-independent algorithm to measure the airway lumen. Their algorithm is an edge detection method based on the “full width at half maximum” principle. They first estimated the luminal perimeter by a hand-drawn line that was then smoothed repeatedly. Multiple lines were then generated perpendicular to the smoothed perimeter, radiating outward away from the lumen into the airway wall and parenchyma. The profile of HU along this line had a minimum in the lumen and a maximum in the soft tissue. The middle value (half maximum) was calculated, and the point on the hand-drawn line was then moved to the half maximum point. This was repeated for all points radiating from the hand-drawn line that now defined the airway luminal perimeter. The advantages of this method are that it is relatively operator-independent and very fast. Nakano et al\textsuperscript{17} improved this method and developed a computer-assisted automated method to measure A\textsubscript{i}, wall thickness, and A\textsubscript{aw}. Reinhardt and colleagues\textsuperscript{18} developed a maximum-likelihood method to estimate the airway inner and outer radius. King and colleagues\textsuperscript{5} reported an automated mum-likelihood method to measure the airway lumen. Their algorithm is an edge detection method based on the principle of score-guided erosion. However, almost all reports to date have been based on identifying cross-sections of airways that appear to be round. Only Wood et al\textsuperscript{15} and King et al\textsuperscript{5} considered, and corrected for, the orientation of angled airways.

Using these HRCT techniques, investigators have assessed airway dimensions in humans. Boulet et al\textsuperscript{27} used an electronic caliper on a CT image, which was displayed at a fixed window and a fixed level to measure airway dimensions manually. They measured airway dimensions in asthmatic subjects and nonasthmatic subjects and expressed the results as the ratio of wall thickness to outer diameter. They found a negative correlation between the thickening of the intermediate stem bronchus and the diameter. They found the results as the ratio of wall thickness to outer radius. King and colleagues\textsuperscript{5} reported an automated mum-likelihood method to estimate the airway inner and outer radius. King and colleagues\textsuperscript{6} measured the change in airway wall and changes throughout the whole bronchial tree. Okazawa and colleagues\textsuperscript{8} studied three groups of asthmatic subjects in 114 smokers (94 COPD patients and 20 asymptomatic control subjects). They found that the A\textsubscript{aw} was increased in patients with asthma without a decrease in A\textsubscript{i} (Table 1). A\textsubscript{aw} decreased in asthmatic subjects (31%) and in normal subjects (27%) in 1,000 g/d of inhaled corticosteroid, the mean airway wall thickness was similar, but it was greater than the mean airway wall thickness of both the control subjects and the asthmatic subjects requiring < 1,000 μg/d of inhaled corticosteroid.

More recently, two papers have been published in which the authors used HRCT and analyzed the airway wall and luminal dimensions of the right upper lobe apical segmental bronchus to examine their relationship with clinical indexes in asthma and COPD.\textsuperscript{10,17} Although the upper lobe apical segmental bronchus is a large airway, it has been shown that the airway dimension of this bronchus correlates well with that of the smaller airways found in CT scans.\textsuperscript{17} Niimi and coworkers\textsuperscript{19} analyzed 51 asthmatic patients (13 mild persistent, 39 moderate persistent, 22 severe persistent, and 7 intermittent) and compared them with 25 healthy volunteers. They found that the A\textsubscript{aw} was increased in patients with asthma without a decrease in A\textsubscript{i} (Table 1). A\textsubscript{aw} coexisted positively with the duration and clinical severity of asthma, while WA% was negatively related to FEV\textsubscript{1} (% predicted), FEV\textsubscript{1}/FVC (%), and forced expiratory flow over the middle half of the vital capacity (% predicted).

Nakano and colleagues\textsuperscript{17} developed customized software to measure the dimensions of the apical segmental bronchi in 114 smokers (94 COPD patients and 20 asymptomatic control subjects). They found that the A\textsubscript{i} was smaller and WA% was bigger in COPD compared with asymptomatic control subjects (Table 2). They tested whether the WA% added value to the prediction of pulmonary function tests beyond a HRCT estimate of the severity of emphysema (percentage of low attenuation area/total lung area × 100; LAA%\textsuperscript{10}). Although both WA% and LAA% correlated with measurements of lung function, the combination of WA% and Aaw/

<table>
<thead>
<tr>
<th>Table 1—Large Airway Dimensions in Asthma Measured Using HRCT*</th>
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<tbody>
<tr>
<td>Control Subjects</td>
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<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Subject Variables</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>FEV\textsubscript{1}, % predicted</td>
</tr>
<tr>
<td>A\textsubscript{i}, mm\textsuperscript{2}</td>
</tr>
<tr>
<td>WA%</td>
</tr>
<tr>
<td>Aaw, mm\textsuperscript{2}</td>
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</tbody>
</table>

*Values given as mean ± SD. Data reprinted with permission from Niimi et al.\textsuperscript{10}

\(p < 0.05\) compared to control.

\(p < 0.05\) compared to subjects with mild persistent asthma.

\(p < 0.05\) compared to moderate persistent asthma.
and LAA% improved the estimate of pulmonary function abnormalities. In a multivariate model, they found that they could more accurately predict FEV₁, FVC, FEV₁/FVC, and peak expiratory flow, but not diffusing capacity of the lung for carbon monoxide, when both the estimate of airway wall thickening and the extent of low attenuation areas were included in a statistical model (Table 3). They also found that they could divide COPD patients into groups who had predominant loss of lung attenuation or thickening and narrowing of the apical segmental bronchus using LAA% and WA% (Fig 3). Although many subjects had both decreased lung attenuation consistent with emphysema and airway wall thickening, there were individuals with similar degrees of obstruction whose abnormalities appeared to be predominantly the results of airway remodeling and others in whom abnormalities appeared to be predominantly related to the loss of lung parenchyma. Interestingly, Nakano et al.¹⁷ found that the luminal area was related to FEV₁, while Niiimi et al.¹⁸ failed to find any relationship of the luminal area with the severity of asthma. The different pattern of remodeling shown by these two studies may reflect fundamental differences in the inflammatory processes in asthma and COPD and could influence the reversibility of the narrowing.

Despite the effort of many investigators, there are still many questions to be answered before the HRCT assessment of airway dimensions can be used as a research or clinical tool to study airway disease. The issues that require further study include the influence of reconstruction algorithm, field of view, and imaging parameters such as scanning amperage, scanning voltage, and helical scanning. The new generation of multi-slice CT scanners have just started to be used, but they promise to make the measurements faster and more accurate.¹⁹ With additional advances in technology, it is likely that quantitative assessment of airway wall dimensions will ultimately provide a valuable tool for the study of airway disease.

Table 2—Large Airway Dimensions in COPD Measured Using HRCT*

<table>
<thead>
<tr>
<th>Subject Variables</th>
<th>Control (n = 20)</th>
<th>COPD (n = 94)</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>64 ± 17</td>
<td>69 ± 7</td>
</tr>
<tr>
<td>Smoking, pack · years</td>
<td>58 ± 45</td>
<td>74 ± 42</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>100 ± 13</td>
<td>37 ± 151</td>
</tr>
<tr>
<td>Ai, mm²</td>
<td>22 ± 6</td>
<td>16 ± 8;</td>
</tr>
<tr>
<td>WA%</td>
<td>59 ± 5</td>
<td>66 ± 8;</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD. Data modified with permission from Nakano et al.¹⁷

Table 3—Correlation Coefficients (r values) of Univariate and Stepwise Multiple Regression Analyses for Pulmonary Function Tests*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate Regression Analysis</th>
<th>Multiple Regression Analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>LAA%</td>
<td>WA%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LAA% and WA%</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>-0.1591</td>
<td>-0.4371</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>-0.5291</td>
<td>-0.3381</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>-0.6501</td>
<td>-0.1921</td>
</tr>
<tr>
<td>PEFR, % predicted</td>
<td>-0.3091</td>
<td>-0.4871</td>
</tr>
<tr>
<td>RV/TLC, %</td>
<td>0.3781</td>
<td>0.4221</td>
</tr>
<tr>
<td>DLCO/VA, mL/min/mm Hg/L</td>
<td>-0.6851</td>
<td>0.0301</td>
</tr>
</tbody>
</table>

*PEFR = peak expiratory flow rate; RV/TLC = residual volume/total lung capacity; DLCO/VA = diffusing capacity of the lung for carbon monoxide/alveolar volume; NA = stepwise multiple regression analysis showed no additional predictive value of including WA%.

Data reprinted with permission from Nakano et al.¹⁷

†Not significant. p Values were adjusted for multiple comparisons. 1p < 0.01.

Figure 3. Relationship between WA% and extent of emphysema (LAA%) in 94 COPD patients and 20 asymptomatic smokers. Horizontal line shows the mean ± 2SD of LAA% of the asymptomatic smokers. Vertical line shows the mean ± 2SD of WA% of the asymptomatic smokers. Using these cutoff values, COPD patients can be divided into groups: airway remodeling-dominant group (high WA% and low LAA%), emphysema-dominant group (low WA% and high LAA%), and a mixed group (high WA% and high LAA%).

REFERENCES
2. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. This official statement was adopted by the ATS Board of Directors, November 1986. Am Rev Respir Dis 1987; 136:225–244
Fibronectin Matrix Deposition and Cell Contractility*

Implications for Airway Remodeling in Asthma

Denise C. Hocking, PhD

The adhesion of cells to the extracellular matrix (ECM) protein, fibronectin, is important in the regulation and coordination of such complex processes as cell growth, migration, differentiation, and ECM organization. The deposition of fibronectin into the ECM is a cell-dependent process that is normally tightly regulated to ensure controlled matrix deposition. Increased deposition of fibronectin and collagen into the subepithelial space of the airways is observed in all forms of asthma and occurs early in the progression of the disease. Experimental evidence suggests a model in which fibronectin matrix accumulation contributes to the progression of asthma by altering both the structural properties of the airways and the functional properties of cells of the airway wall.

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**Key words:** asthma; collagen; contractility; extracellular matrix; fibronectin; migration

**Abbreviations:** ECM = extracellular matrix; GST = glutathione-S-transferase; III-1H = cryptic, heparin-binding, C-terminal III-1 fragment

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**Fibronectin Matrix Deposition and Cell Contractility**

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**ECM Organization and Asthma**

The mechanism by which enhanced ECM deposition contributes to the pathogenesis of asthma is not known. It has been proposed that the increased deposition of fibronectin and collagen into the subepithelial matrix alters the precise molecular composition of the airway and thereby affects both the geometric and biomechanical...