The changes in airways structure associated with reduced forced expiratory volume in one second


The changes in airways structure associated with reduced forced expiratory volume in one second. K. Matsuba, J.L. Wright, B.R. Wiggs, P.D. Pare, J.C. Hogg.

ABSTRACT: We compared the structure of the membranous and respiratory bronchioles of resected lungs from 111 patients with a normal predicted forced expiratory volume in one second (FEV₁) to the structure of these airways from 45 patients with an FEV₁ reduced below the 95% confidence limits for height and age. Membranous and respiratory bronchioles of less than 2 mm in internal diameter were counted and their diameter and wall thickness were measured. The data show that there were more membranous bronchioles of internal diameter less than 0.4 mm in patients with reduced FEV₁. The wall thickness of respiratory bronchioles was increased in the obstructed group and there was also an increase in the ratio of wall thickness to lumen diameter in these airways. The walls of membranous bronchioles were not increased in thickness but there was an increase in the ratio of wall thickness to lumen diameter. Although the data is consistent with the hypothesis that airways obstruction in patients with chronic obstructive pulmonary disease is due to thickening of the airway wall and narrowing of the airway lumen, we cannot rule out distortion of the membranous bronchioles by loss of elastic recoil.

The present study addressed the problem of the relative importance of these two processes in obstructive lung disease. In particular we measured wall thickness and lumen diameter in small airways of patients with obstructive lung disease and similarly aged smokers without airflow obstruction. These data were then analysed to determine whether or not the changes in wall thickness associated with airway narrowing could be explained by a loss of airway support.

** Methods

The patient population consisted of 120 males and 36 females who had resection of a lung or lobe because of a peripheral pulmonary nodule. One hundred and forty seven of the 156 patients were smokers and all required lung resection because of malignant disease. Prior to operation, all of the patients answered a questionnaire concerning smoking and occupational history, with the assistance of a knowledgeable person. Patients who had been employed for one or more years as a coal miner, welder, foundry worker, hard rock miner or asbestos insulation worker were excluded. Additional exclusion criteria included patients who, on roentgenographic examination, had an obstructive pneumonitis involving...
more than one lobar segment. In addition, at the time of pathological examination or bronchoscopy, if there was obstruction of a segmental or larger airway in the resected lobe or lung, the patients were not included.

**Physiology**

Pulmonary function was measured within 7 days of surgery in all patients. Maximal expiratory flow rates and forced vital capacity were measured with a 91 Stead-Wells spirometer, or a Collins computerized spirometer. The forced expiratory volume in one second (FEV$_1$) was measured directly from spirometer tracings and expressed as a percentage of the predicted value using the prediction equation of Morris et al. [9].

**Pathology**

The specimens were obtained from the operating room and were inflated with 10% buffered formalin or 3% buffered glutaraldehyde at a pressure of 25 cmH$_2$O and allowed to fix for 24 h. After fixation, the specimens were cut into 1 cm thick sagittal slices and routine pathological examination was completed. A mid-sagittal slice was used to assign an emphysema score based on a modification [10] of the method of Thurlbeck et al. [11]. Five or six stratified random blocks of tissue were obtained from the medial and lateral sagittal slices of each specimen using a template of known size. The blocks were processed in the usual fashion, 5 μm sections were cut and stained with haematoxylin-eosin. Final tissue area was measured using a digitizer and outlining the tissue on the histological slide.

All noncartilaginous airways less than 2 mm in internal diameter were identified under the microscope and defined as membranous bronchioles (MB: nonalveolated airways) or respiratory bronchioles (RB: partially alveolated airways). Internal diameter, from basement membrane to basement membrane, and external diameter, between the two adventitial borders, were measured using a computer controlled digitizer. If more than one half of an RB was entirely alveolated, it was regarded as an alveolar duct and excluded. For ellipsoid sections the measured diameter was the maximal diameter perpendicular to the longitudinal axis. The airway wall thickness was calculated as half of the difference between external diameter and internal diameter. All values were corrected for shrinkage during tissue processing, calculated as the square root of the ratio of initial to final tissue area.

**Data analysis**

Using the prediction equation of Morris et al. [9] the height corrected FEV$_1$ was calculated for each subject and plotted against age for both males and females. Figure 1 shows the regression line and the 95% confidence limits of the predicted data of Morris et al. [9]. One hundred and eleven cases were within the 95% confidence limits (normal group, mean FEV$_1$ 91.2%) and 45 cases were below the lower 95% confidence limit (obstructed group, mean FEV$_1$ 67.9%). The distributions of internal diameters and the ratio of wall thickness to internal diameter for each airway type in the normal and the obstructed group were compared using the two sample Kolmogorov-Smirnov test. Differences in mean

![Graph](image-url)

*Fig. 1.* The study population was divided into two groups based on whether the height corrected forced expiratory volume in one second (FEV$_1$) was within or outside of two standard deviations of the regression line representing the relationship between FEV$_1$ and age according to the equation of Morris et al. [9]. In order to correct for the coupling of FEV$_1$ with height, we subtracted from each patient's FEV$_1$ the estimated height contribution determined from the Morris equation. The Y-axis therefore represents the equation:

\[
\text{measured FEV}_1 - \text{height} \times 0.092/2.54 \text{ (males)}
\]
\[
\text{measured FEV}_1 - \text{height} \times 0.089/2.54 \text{ (females)}
\]

The values for the Y-axis are thus expressed as height corrected FEV$_1$, with the value in litres.
morphometric data were compared between normal and obstructed groups using a two-sample t test. For all analyses, values of p<0.05 were considered to be significant.

Results

Age, smoking history, emphysema scores and lung function for the normal and obstructed groups are shown in Table 1. There was no significant difference in age between the 111 patients in the normal group and the 45 patients in the obstructed group. The obstructed group had smoked more than the normal group (p<0.01) and had emphysema scores that were slightly higher (p<0.01).

It is important to note that airway narrowing, like emphysema, does not occur in a regular fashion. Therefore, the mean values for internal diameter or wall thickness can be altered in a major fashion simply by the inclusion or omission of a very few abnormal airways. Significant overall abnormalities can only be assessed by utilizing all of the airway measurements. It is for this reason that we have chosen to depict our data using the cumulative distribution curves. The mean data are given in Table 2, to provide comparisons with other investigators work, and show internal diameter, wall thickness, and the ratio of wall thickness to internal diameter for each airway type in the normal and obstructed patients.

There were 1,218 MB and 1,076 RB examined in the normal group, and 523 MB and 563 RB examined in the obstructed group. The mean internal diameter of the MB was narrowed (p<0.001) in the obstructed group, while the mean internal diameter for RB was no different. Although the mean wall thickness of MB was no different between the two groups, the respiratory bronchioles in the obstructed group had an increased mean wall thickness (p<0.01) and an increased wall thickness to internal diameter ratio (p<0.01).

Table 1. - Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Normal group</th>
<th>Obstructed group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>111</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>61±12</td>
<td>61±10</td>
<td></td>
</tr>
<tr>
<td>FEV, % pred</td>
<td>91.2±11.5</td>
<td>67.9±11.0</td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td>45±35 (0-144)</td>
<td>60±31 (6-106)</td>
<td>0.01</td>
</tr>
<tr>
<td>Emphysema score</td>
<td>10.7±13.9 (0-70)</td>
<td>18.8±21.3 (0-80)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Values are mean±so. Brackets indicate range of data. Normal group: FEV, within 95% of CL; obstructed group: FEV, below the lower 95% of CL; FEV: forced expiratory volume in one second; FEV, % pred: FEV, as a percentage of predicted value; CL: confidence limit; smoking history: pack-years; emphysema score: numerical value assigned as described in [10, 11].

Table 2. - Mean morphological data

<table>
<thead>
<tr>
<th></th>
<th>Normal group n=111</th>
<th>Obstructed group n=45</th>
</tr>
</thead>
<tbody>
<tr>
<td>MB</td>
<td>RB</td>
<td>MB</td>
</tr>
<tr>
<td>Internal diameter</td>
<td>0.54±0.02</td>
<td>0.45±0.01</td>
</tr>
<tr>
<td>Wall thickness</td>
<td>0.18±0.01</td>
<td>0.11±0.002</td>
</tr>
<tr>
<td>Wall thickness/ID</td>
<td>0.43±0.04</td>
<td>0.31±0.02</td>
</tr>
</tbody>
</table>

Values are mean±so. ***: p<0.001; **: p<0.01; *: p=0.06; MB: membranous bronchiole; RB: respiratory bronchiole; ID: internal diameter. Data are the composite mean values from all airways in each patient.
Figure 2 shows the cumulative frequency distributions of the internal diameter of the airways and indicates that MB (fig. 2A; p<0.001) but not RB (fig. 2B) are significantly shifted to smaller internal diameters in the obstructed group of patients. In the normal group, 36.0% of MB were less than 0.4 mm, while in the obstructed group 54.5% were in this size range.

Figure 3 shows a cumulative distribution of the ratio of wall thickness to internal diameter for both membranous (fig. 3A) and respiratory (fig. 3B) bronchioles. The ratio of wall thickness to internal diameter was shifted (p<0.01) to the right in the obstructed group, indicating excess wall thickening for a given diameter.

Fig. 2. - The cumulative frequency distribution of airway internal diameter is indicated, comparing the normal group to the obstructed group. Figure 2A shows the data for membranous bronchioles, and figure 2B the data for respiratory bronchioles.

Fig. 3. - The cumulative distributions of the ratio of wall thickness to internal diameter are shown, comparing the normal and obstructed groups. Figure 3A demonstrates the data for membranous bronchioles and figure 3B the data for respiratory bronchioles.
Discussion

We used FEV₁ predicted as a marker of airflow obstruction. The FEV₁ is the most widely used test that reflects the resistance to airflow within the airways, and a diminished FEV₁ at age 60 yrs in a smoker suggests that the individual is one of the subset of susceptible smokers who develop a rapid decline in FEV₁, and eventual symptomatic COPD [12]. Indeed, Higgins et al. [13] have suggested that this distinction can be made at a very early age. Prospective studies have clearly established the accuracy of FEV₁ in estimating the risk of premature morbidity [14, 15].

A current concept for the pathogenesis of emphysema suggests that there is a relative excess of proteases, particularly elastase, in the lung tissue of smokers. This leads to destruction of lung connective tissue, disruption of alveolar walls and enlargement of airspace, producing the characteristic gross findings of emphysematous lung destruction. The decreased lung elasticity and destruction of the alveolar support of the airway walls could also theoretically produce airways narrowing, and McConnell et al. [16] suggested that this subsequent tortuosity and collapse would produce increased airways resistance and clinical airflow obstruction. However, when this hypothesis was tested by direct measurements of peripheral airway resistance in lungs with airflow obstruction [1], resistance did not decrease to normal levels when lung volume was increased as would be expected if loss of recoil was the only important mechanism of airway narrowing. Similarly, these studies [1] showed that there was no evidence for increased peripheral airways resistance during deflation as might be expected if loss of alveolar support caused the peripheral airways to behave as a check valve. Although a number of subsequent studies have provided data suggesting that loss of elastic recoil or destruction of alveolar support [17–19] caused airways obstruction, none of these studies have attempted to assess the effects of these changes by direct measurements of peripheral airways resistance.

In previous studies, we [20] and others [21–23] used a grading system to show that patients with airflow obstruction have an increase in airway wall fibrosis and inflammatory cells. We also demonstrated that patients who smoke or have smoked show thickening of their airways which appears to be independent of the presence of emphysema [23]. There are, however, no studies which have made measurements of the airway walls and correlated these data directly to abnormalities of airflow obstruction.

As noted above, emphysematous destruction of alveoli could secondarily narrow the airways. In the present study, we found an overall narrowing of the membranous bronchioles in the obstructed group, data consistent with this explanation. Since, in this situation, one would expect an increase in airway wall thickness simply because the tissue mass would remain constant, the ratio of wall thickness to internal diameter would also be shifted toward the right as is apparent from figure 2. Therefore, in this study, we cannot conclude that the increased airway wall thickness seen in the membranous bronchioles is not due in part to alteration of elastic recoil.

However, we also found a shift in the ratio of wall thickness/internal diameter in the respiratory bronchioles of the obstructed group compared to the non-obstructed group, data which would suggest that there was an actual increase in tissue volume within the airway wall since these airways were not noted to be narrowed. This increase in wall thickness is attributed to a chronic inflammatory process with its associated oedema, cellular infiltration and connective tissue deposition.

In summary, our data show that patients with airflow obstruction have respiratory bronchioles with thickened walls and membranous bronchioles with narrowed lumens. Although it appears that smoking produces an inflammatory reaction in the airway wall with resultant fibrosis, distortion, and airflow obstruction, we cannot rule out distortion of the membranous bronchioles as a result of alveolar wall destruction and loss of elastic recoil.

References

14. Petty TL, Good JT, White DP. – Long-term follow-up of a random population observed for the prevalence and outcome
FEV1 AND SMALL AIRWAY STRUCTURE


RÉSUMÉ: Nous avons comparé la structure des bronchioles membraneuses et respiratoires de poumons réséqués chez 111 patients dont le VEMS était normal, à celle des mêmes voies aériennes provenant de 45 patients dont le VEMS était inférieur aux limites de confiance de 95% pour leur taille et leur âge.

L'on a fait le décompte des bronchioles membraneuses et respiratoires de moins de 2 mm de diamètre interne, et l'on a mesuré leur diamètre et l'épaisseur de leurs parois. Les données montrent que chez les patients dont le VEMS est diminué, le nombre de bronchioles membraneuses dont le diamètre interne est inférieur à 0.4 mm est augmenté. L'épaisseur des parois des bronchioles respiratoires est augmentée dans le groupe avec obstruction, de même que le rapport de l'épaisseur de la paroi au diamètre de la lumière des mêmes voies aériennes. Les parois des bronchioles membraneuses ne sont pas épaissies, mais il y a une augmentation du rapport de l'épaisseur de la paroi au diamètre de la lumière. Quoique ces données soient en accord avec l'hypothèse que l'obstruction des voies aériennes chez les patients atteints de maladie pulmonaire chronique obstructive est due à un épaississement de la paroi des voies aériennes et à un rétrécissement de leur lumière, nous ne pouvons pas exclure le rôle éventuel d'une distorsion des bronchioles membraneuses par perte de leur capacité de recul élastique.

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