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Quality, Size, and Composition of Pediatric Endobronchial Biopsies in Cystic Fibrosis*

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Background: Studies on airway remodeling in children with cystic fibrosis (CF) may be hampered by difficulty in obtaining evaluable endobronchial biopsy specimens because of large amounts of mucus and inflammation in the CF airway. We prospectively assessed how the quality of biopsy specimens obtained from children with CF compare with those from children with other airway diseases.

Methods: Fiberoptic bronchoscopy with endobronchial biopsy was performed in 67 CF children (age range, 0.2 to 16.8 years), 34 children with wheeze/asthma (W/A), and 64 control children with chronic respiratory symptoms. Up to three biopsy specimens were taken and stained with hematoxylin and eosin. Biopsy specimen size and structural composition were quantified using stereology.

Results: At least one evaluable biopsy specimen was obtained in 72% of CF children, in 79% of children with W/A, and in 72% of control subjects (difference was not significant). The use of large biopsy forceps (2.0 mm) rather than small biopsy forceps (1.0 mm) [odds ratio (OR), 5.8; 95% confidence interval (CI), 1.1 to 29.8; p = 0.037] and the number of biopsy specimens taken (odds ratio, 2.6; 95% confidence interval, 1.3 to 5.2; p = 0.006) significantly contributed to the success rate. Biopsy size and composition were similar between groups, except that CF children and those patients with W/A had a higher percentage of the biopsy specimen composed of muscle than did control subjects (median 6.2% and 9.7% vs 0.9%, respectively; p = 0.002).

Conclusions: Biopsy size and quality are adequate for the study of airway remodeling in CF children as young as 2 months of age. Researchers should use large forceps when possible and take at least two biopsy specimens per patient. An increased airway smooth muscle content of the airway mucosa may contribute to the pathophysiology of CF lung disease.

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Key words: airway remodeling; airway smooth muscle; biopsy; child; cystic fibrosis

Abbreviations: CF = cystic fibrosis; W/A = wheeze/asthma

Although infants with cystic fibrosis (CF) are born with structurally normal lungs, respiratory dysfunction often develops in the first years of life and is progressive.1,2 Early death from respiratory failure is due predominantly to extensive structural airway changes (hereafter referred to as remodeling), with widespread bronchiectasis, cyst formation, mucoid impaction, atelectasis, fibrosis, and vascular changes.3,4 To date, most work on airway wall pathology in patients with CF has been performed using end-stage lungs at autopsy or at the time of transplantation. Therefore, little is known about the natural history of CF lung disease, in particular about the early stages of CF airway pathology.

Studies in asthma involving endobronchial biopsy have allowed detailed investigation of remodeling and inflammation in children.5–8 The safety of performing endobronchial biopsy in infants and small children, including those with CF, has been demonstrated.9–11 However, it is not known whether study-
ing airway remodeling in CF children could be hampered by the difficulty of visualizing a clear airway and obtaining tissue of adequate size and quality because of the large amounts of mucus in the CF airway or because inflammation renders the mucosa friable. It could be hypothesized that biopsy forceps would slip on the CF mucosa instead of grasping it firmly, thus yielding only small amounts of biopsy tissue composed mainly of epithelial strips with little subepithelial stroma.

The aim of the present study, which was carried out in the context of a larger study investigating the relationship of inflammation, infection, and structural airway wall changes in patients with CF, was to investigate whether biopsy specimens obtained from children with CF were of sufficient quality to study airway remodeling. In particular, we wished to answer the following questions: (1) In what proportion of children with CF can an evaluable biopsy specimen be obtained compared to that in groups of patients with other diseases (eg, wheeze and asthma, in which remodeling has already been studied)? (2) Which factors predict the likelihood of obtaining an evaluable biopsy specimen? and (3) Are the size and composition of CF biopsy specimens similar to those obtained in children with other diseases? Our preliminary results have been reported previously in abstract form.12

**Materials and Methods**

**Subjects**

The present prospective study included 165 children who had clinically indicated flexible bronchoscopy performed between February 2003 and November 2005, and in whom an attempt was made to obtain an endobronchial biopsy specimen for the purpose of research. There were 67 children with CF (ie, the CF group), 34 children investigated for recurrent wheeze or difficult asthma (ie, the wheeze/asthma [W/A] group), and 64 children investigated because of other chronic respiratory symptoms in whom a diagnosis of CF had been excluded and who did not have any history of wheeze or atopy (ie, the control group) [Table 1]. The diagnosis of CF and asthma were made according to standard criteria.13,14 Children with wheeze and children with chronic respiratory symptoms had been referred to a tertiary center for investigation and underwent bronchoscopy as part of their clinical assessment. Some of the CF children included in this study have been previously reported on in a study11 demonstrating the safety of obtaining endobronchial biopsy specimens in children with CF, and some of the biopsy specimens from the children in the W/A group have been included in studies on airway remodeling in asthma.15,16 Informed consent for the procedure was obtained from the parents of all children. The study was approved by the Royal Brompton & Harefield NHS Trust Ethics Committee.

**Flexible Bronchoscopy**

All bronchoscopies were performed under general anesthesia as previously described.17 Several different bronchoscopes (BF-XP40 [2.8 mm external diameter]; Olympus; Tokyo, Japan; or BF-3C20 or 3C40 [3.6 mm external diameter], BF-MP60 videobronchoscope [4.0 mm external diameter], or BF-P20D [4.9 mm external diameter]; KeyMed; Southend-on-Sea, Essex, UK) were used, depending on the size of the child. Up to three endobronchial biopsy specimens were taken under direct vision from a standardized site (ie, subsegmental bronchi of the right lower lobe). Small reusable forceps (FB-56D, oval cup with rat tooth jaw; KeyMed) were used with the 2.8-mm or 3.6-mm bronchoscope (both with a 1.2-mm working channel). Large reusable forceps (FB-19-C1, oval cup standard; KeyMed) or single-use forceps (FB-231D, oval cup standard; KeyMed) were used with the 4.0-mm or 4.9-mm bronchoscope (working channel, 2.0 vs 2.2 mm, respectively).

**Biopsy Processing**

Biopsy specimens were fixed in 10% formal saline solution overnight and processed to paraffin wax. Up to 10 sections with a thickness of 3 μm were obtained at 25-μm to 50-μm intervals, dependent on biopsy size, and were stained using hematoxylin-eosin.

**Evaluable Biopsy Specimens**

One section of each biopsy specimen was selected and assessed by an observer (N.R.), who was blinded to the child’s diagnosis, for the presence or absence of the following structures: epithelium; reticular basement membrane; subepithelial stroma; smooth muscle; submucosal glands; and other aspects, including vessels, cartilage, crush, “space,” edema, and blood. Each biopsy specimen was then categorized as “nonevaluable” or “evaluable.” To be categorized as evaluable, a biopsy specimen had to fulfill the following criteria: (1) presence of epithelium, reticular basement membrane, and subepithelial stroma, without requirement of minimal tissue quantity; (2) good orientation; and (3) minimal crush, edema, or blood within the biopsy specimen.

**Size and Composition of Biopsy Specimens**

The biopsy area and structural composition (ie, the percentage of the biopsy specimen composed of epithelium, reticular base-
ment membrane, subepithelial stroma, smooth muscle, submu-
cosa sal glands, and other features) were quantified using the
stereologic technique of point counting.5 The areas of the
structures of interest were determined at a magnification of
200 with the aid of an eyepiece graticule containing 100 points, and
the data were expressed as a percentage of the whole biopsy
specimen area. The biopsy specimen area was calculated as
follows: area (in square millimeters) = number of points counted × 0.0016. Intraobserver repeatability was assessed by measuring
the same section four times, with the result expressed as the
percentage coefficient of variation.

Statistical Analysis
Nonparametric tests were applied to test for intergroup differ-
ences, first with the Kruskal-Wallis test, followed, if a significant
difference (p < 0.05) was found, by Mann-Whitney U tests for
between-group comparisons.18 The Bonferroni correction was
made for multiple comparisons.18 Associations were looked for by
Spearman rank correlation. The χ² test was used to test for
differences in the distribution of categoric variables. Logistic
regression was used to perform multivariate analysis. A statistical
software package (SPSS, version 12; SPSS; Chicago, IL) was used
for statistical analysis.

Results
Bronchoscopies
Demographics for the 165 children and the pri-
mary clinical reason for bronchoscopy are summa-
rized in Table 1. Median age was not significantly
different between groups.
The bronchoscopies were undertaken by five
bronchoscopists who performed 81 procedures
(49%), 44 procedures (27%), 32 procedures (19%), 7
procedures (4%), and 1 procedure (1%). A 2.8-mm
bronchoscope was used in 23 cases (14%), a 3.6-mm
bronchoscope was used in 68 cases (41%), a 4.0-mm
bronchoscope was used in 16 cases (10%), and a
4.9-mm bronchoscope was used in 57 cases (35%).
In one case, the bronchoscope used was not re-
corded. The size of the forceps used did not differ
significantly between patient groups. The large for-
ceps were used in 37 CF patients (55%), in 12 W/A
patients (36%), and in 24 control subjects (38%).
When using the large forceps, the bronchoscopist
had the choice of a reusable pair (21 cases) or a
disposable pair (43 cases). In nine cases, the forceps
type was not recorded. One biopsy specimen was
obtained in 9 cases (5%), two biopsy specimens were
obtained in 17 cases (10%), and three biopsy speci-
mens were obtained in 127 cases (77%). In eight
cases (seven CF children and one control subject),
no biopsy specimen was taken at the decision of the
individual bronchoscopist, mainly due to the proce-
dure having lasted a considerable amount of time.
In four cases, the number of biopsy specimens taken
was not recorded. None of the 165 children experi-
enced complications such as significant bleeding or
pneumothorax during or after the procedure.
Evaluable Biopsy Specimens
Overall, at least one evaluable biopsy specimen
was obtained in 121 of the 165 children (73%) in
whom an attempt was made to take an endobron-
chial biopsy specimen. As shown in Table 2, success
rates were similar between patient groups. The
youngest child in whom an evaluable biopsy speci-
men was obtained was a 2-month-old CF infant. In
CF children < 4 years old, at least one evaluable biopsy specimen was obtained in 13 of 23 children (57%). Figure 1 shows a biopsy specimen from a CF child.

The probability of obtaining at least one evaluable biopsy specimen was mainly dependent on the size of the forceps used (large forceps, 93% success rate; small forceps, 57% success rate; p < 0.001) [Table

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<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases With at Least One Evaluable Biopsy Specimen</th>
<th>CF Patients</th>
<th>W/A Patients</th>
<th>Control Subjects</th>
<th>Overall p Value†</th>
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</thead>
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<tr>
<td>Diagnosis group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CF patients (n = 67)</td>
<td>48 (72)</td>
<td>24 (45)</td>
<td>19 (55)</td>
<td>22 (71)</td>
<td>0.67</td>
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<tr>
<td>W/A patients (n = 34)</td>
<td>27 (79)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control subjects (n = 64)</td>
<td>46 (72)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchoscopist</td>
<td></td>
<td></td>
<td></td>
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<td>0.21†</td>
</tr>
<tr>
<td>Consultant A (n = 81)</td>
<td>65 (80)</td>
<td>24 (80)</td>
<td>19 (45)</td>
<td>22 (71)</td>
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</tr>
<tr>
<td>Consultant B (n = 44)</td>
<td>31 (71)</td>
<td>13 (77)</td>
<td>7 (58)</td>
<td>11 (73)</td>
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<tr>
<td>Consultant C (n = 32)</td>
<td>21 (66)</td>
<td>7 (54)</td>
<td>1 (50)</td>
<td>13 (77)</td>
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<tr>
<td>Consultant D (n = 7)</td>
<td>4 (57)</td>
<td>4 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>Consultant E (n = 1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>Forceps size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Small, 1.0 mm (n = 91)</td>
<td>52 (57)</td>
<td>16 (53)</td>
<td>14 (67)</td>
<td>22 (55)</td>
<td></td>
</tr>
<tr>
<td>Large, 2.0 mm (n = 73)</td>
<td>68 (93)</td>
<td>32 (87)</td>
<td>12 (100)</td>
<td>24 (100)</td>
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<tr>
<td>Type of large forceps</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.06</td>
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<tr>
<td>Disposable (n = 43)</td>
<td>42 (98)</td>
<td>18 (98)</td>
<td>9 (100)</td>
<td>15 (100)</td>
<td></td>
</tr>
<tr>
<td>Reusable (n = 21)</td>
<td>18 (86)</td>
<td>8 (73)</td>
<td>3 (100)</td>
<td>7 (100)</td>
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</tr>
<tr>
<td>Biopsy specimens obtained</td>
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<td></td>
<td></td>
<td></td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>One (n = 9)</td>
<td>4 (44)</td>
<td>1 (50)</td>
<td>0 (0)</td>
<td>3 (75)</td>
<td></td>
</tr>
<tr>
<td>Two (n = 17)</td>
<td>13 (77)</td>
<td>2 (67)</td>
<td>9 (100)</td>
<td>2 (40)</td>
<td></td>
</tr>
<tr>
<td>Three (n = 127)</td>
<td>102 (80)</td>
<td>45 (82)</td>
<td>18 (82)</td>
<td>39 (78)</td>
<td></td>
</tr>
<tr>
<td>Year of bronchoscopy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>2003 (n = 84)</td>
<td>57 (68)</td>
<td>19 (63)</td>
<td>21 (81)</td>
<td>17 (61)</td>
<td></td>
</tr>
<tr>
<td>2004 (n = 39)</td>
<td>30 (77)</td>
<td>15 (79)</td>
<td>4 (67)</td>
<td>11 (79)</td>
<td></td>
</tr>
<tr>
<td>2005 (n = 42)</td>
<td>34 (81)</td>
<td>14 (78)</td>
<td>2 (100)</td>
<td>18 (82)</td>
<td></td>
</tr>
</tbody>
</table>

*Values are given as No. (%), unless otherwise indicated. Totals include all children in whom an attempt was made to take an endobronchial biopsy.
†By χ² test.
‡With the exclusion of consultants D and E.

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Figure 1. Low-power view of an endobronchial biopsy section from a 9-year-old CF child (hematoxylin-eosin, original × 50).
The success rate also was higher if more than one biopsy specimen was taken, and if disposable forceps, compared to reusable forceps, were used. There was also a small operator effect (i.e., the highest success rate was for the most experienced bronchoscopist) and an effect of the year in which the bronchoscopy was performed (improvement with time). However, the probability of obtaining at least one evaluable biopsy specimen did not depend on the child’s diagnosis.

Logistic regression was used to perform multivariate analysis with variables entered including the following: “diagnosis group”; “bronchoscopist”; “forceps size”; “forceps type”; “number of biopsy specimens taken”; and “year of bronchoscopy.” Both the use of a large forceps (odds ratio, 5.8; 95% confidence interval, 1.1 to 29.8; p = 0.04) and the number of biopsy specimens taken (odds ratio, 2.6; 95% confidence interval, 1.3 to 5.2; p = 0.006) remained significantly associated with the probability of obtaining at least one biopsy specimen considered as evaluable.

Size and Composition of Biopsy Specimens

To compare the size and composition of biopsy specimens among patient groups, children matched for forceps size and adjusted for the number of biopsy specimens taken, the type of large forceps, and patient age were selected from each group; this led to 24 children in each disease group being included in this part of the study. Fourteen patients in each group had had a biopsy specimen taken with small forceps, and 10 patients had had one taken with large forceps. In cases in which more than one evaluable biopsy specimen was available for a given patient, the largest of the biopsy specimens was chosen for intergroup comparison.

As might be expected, the overall area of the biopsy specimen was larger if it had been taken with large forceps compared to small forceps, although the numbers were too small to reach statistical significance (large forceps: median biopsy specimen area, 0.56 mm$^2$; range, 0.23 to 1.45 mm$^2$; small forceps: median biopsy specimen area, 0.34 mm$^2$; range, 0.1 to 0.95 mm$^2$; p = 0.09) [Fig 2, left, A]. The area of the biopsy specimen was comparable among the three groups of patients (CF patients: median area, 0.36 mm$^2$; range, 0.17 to 1.28 mm$^2$; W/A patients: median area, 0.49 mm$^2$; range, 0.10 to 1.40 mm$^2$; control subjects: median area, 0.42 mm$^2$; range, 0.15 to 1.45 mm$^2$) [Fig 2, right, B].

The composition of the biopsy specimens was similar among groups for all structures, except for smooth muscle. Biopsy specimens obtained from children with CF and W/A had a higher percentage composed of muscle than did those from control subjects (children with CF: median biopsy specimen area occupied by muscle, 6.2%; range, 0 to 19.2%; children with W/A: median biopsy specimen area occupied by muscle, 9.7%; range, 0 to 23.7%; control subjects: median biopsy specimen area occupied by muscle, 0.9%; range, 0 to 16.8%; p = 0.002) [Fig 3]. The median subepithelial stroma area was similar among groups (children with CF: median area, 0.25 mm$^2$; range, 0.04 to 1.3 mm$^2$; children with W/A: median area, 0.22 mm$^2$; range, 0.04 to 0.78; control subjects: median area, 0.23 mm$^2$; range, 0.1 to 0.84 mm$^2$).

The intraobserver repeatabilities, expressed as the percentage coefficient of variation in two different

![Figure 2](https://www.chestjournal.org/figure2.png)
biopsy specimens, were 3% and 7% for biopsy specimen area, and ranged from 2% (epithelium) to 9% (submucosal glands) for the structures of interest (ie, epithelium, reticular basement membrane, subepithelial stroma, smooth muscle, submucosal glands, and others).

**DISCUSSION**

The present prospective study shows that, as with pediatric asthma, endobronchial biopsy specimens obtained from children with CF are of sufficient quality to study airway remodeling. At least one evaluable biopsy specimen was obtained in three quarters of the children studied, some as young as a few months of age, independently of diagnostic group. Biopsy specimens obtained from CF children were comparable in size and composition to those from children with other respiratory conditions, and allowed identification of the epithelium, the reticular basement membrane, the subepithelial stroma, smooth muscle, and mucus-secreting glands.

The performance of endobronchial biopsy in CF children was difficult in some cases, mainly because of mucus obscuring the view through the bronchoscope, and because of the difficulty of getting the forceps to grip sufficiently well on a subcarina. Indeed, in seven children with CF, but in only one control child, no biopsy specimen could be obtained. Nevertheless, the overall proportion of evaluable biopsy specimens obtained was similar in children with CF compared to the groups of children with other diseases, even with the inclusion of the children in whom no biopsy specimen could be obtained for analysis.

Our data show that the probability of obtaining at least one evaluable biopsy specimen per child is increased if at least two biopsy specimens are taken and if large forceps are used. The size of the forceps depends on the size of the bronchoscope used, which is determined by the size of the child. Bronchoscopes with small working channels, and therefore small forceps, have to be used in children under approximately 3 years of age, whereas in older children a bronchoscope with a large working channel and therefore large forceps can be used. Bronchoscopes with a small external diameter/working channel ratio, such as that in the 4.0-mm videobronchoscope used for some children in this study, are therefore recommended for biopsy studies in young children, as they allow more efficient sampling. Our data further support the use of disposable forceps whenever available. The small operator effect that we have found (ie, the operator who had obtained...
the most biopsy specimens had the best result) demonstrates that, as would be expected, experience leads to an improvement in the quality of the sample. This is also shown by the improvement in biopsy specimen quality with time that was seen in this study, although this observation may reflect an increased use of the 4.0-mm bronchoscope in young children in the past few years.

With the exception of the bronchial smooth muscle content, we found that the biopsy specimens were of similar composition in all patient groups. Biopsy specimens from children with CF and W/A had a higher percentage of muscle than those from control children with other mixed airway diseases and no history of wheeze or atopy. These findings add to the findings of previous studies in adults, which have shown airway smooth muscle remodeling both in patients with asthma and in those with CF.

There is considerable inhomogeneity of pathology in the lungs of CF patients. Thus, we acknowledge that the sampling of biopsy specimens from a standardized site (the right lower lobe in our case) may not be representative of the worst affected parts of the bronchial tree. However, all biopsies were performed under direct vision, allowing us to avoid areas that appear macroscopically unrepresentative of the visible bronchial tree. The sampling from possibly less affected regions of the lungs may also overestimate the safety of the procedure. For instance, the safety margin may be reduced by the increase in bronchial blood flow seen in patients with advanced CF lung disease. It is, however, noteworthy that none of the 165 cases studied here experienced complications such as significant bleeding or pneumothorax, confirming the findings of previous reports of the safety of performing endobronchial biopsies in infants and children with and without CF.

As has been discussed in an editorial and rebuttal accompanying our recent report on the safety of endobronchial biopsy specimens in children with CF, it would be unethical to carry out an invasive nontherapeutic research procedure in children without any scientific hypothesis that might lead to new knowledge and then, in turn, to a more general benefit to a patient group. Our scientific hypothesis, which has been the subject of a doctoral thesis and a recent report, was driven, then alternative therapeutic strategies are required. The modulation of structural changes, for example, with macrolide therapy, might be a life-preserving strategy and thus of benefit to CF patients. Clearly, the data reported here as well as previous safety data reported by our group should not be interpreted as encouragement to embark on bronchoscopic biopsy studies wherever available, unless as part of hypothesis-driven research the eventual aim of which is to improve patient care. Since clinical benefit to patients has not been shown yet in either the present study or those of others, we do not at this time recommend the use of bronchial biopsies as a clinical tool in patients with CF.

In conclusion, we have found that airway remodeling can be identified and investigated for the purposes of research in endobronchial biopsy specimens from children with CF; evaluable biopsy specimens can be obtained safely in infants as young as 2 months of age. To increase the likelihood of obtaining an evaluable biopsy specimen for such a purpose, it is preferable to use disposable large forceps (ie, a bronchoscope with a working channel of ≥ 2.0 mm) and to take at least two biopsy specimens. We have found that children with CF have increased smooth muscle content in the airway wall, thus extending previous reported findings of airway smooth muscle remodeling in adults with CF into the pediatric population. These observations may be of relevance to the pathophysiology of CF and need to be investigated formally in a future study.

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