

# Time Required to Obtain Endobronchial Biopsies in Children During Fiberoptic Bronchoscopy

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**Summary.** Background: Endobronchial biopsies are an important tool for the study of airway remodeling in children. We aimed to evaluate the impact of performing endobronchial biopsies as a part of fiberoptic bronchoscopy on the length of the procedure. Methods: Clinically indicated fiberoptic bronchoscopy at which endobronchial biopsy was attempted as a part of a research protocol was performed in 40 children (median age 6 years, range 2 months–16 years). Time needed for airway inspection, bronchoalveolar lavage (BAL) with three aliquots of 1 ml/kg of 0.9% saline, sampling of three macroscopically adequate biopsies, teaching, and other interventions (e.g., removal of plugs) was recorded. The bronchoscopist was not aware that the procedure was being timed. Results: Median (range) duration (min) was 2.5 (1.0–8.2) for airway inspection, 2.8 (1.7–9.4) for BAL, 5.3 (2.5–16.6) for biopsy sampling, 2.4 (1.5–6.6) for teaching and 4.1 (0.8–18.5) for other interventions. Three adequate biopsies were obtained in 33 (83%) children. Use of 2.0 mm biopsy forceps (via 4.0 and 4.9 mm bronchoscopes) rather than 1.0 mm (via 2.8 and 3.6 mm bronchoscopes) significantly reduced biopsy time (4.6 min vs. 8.4 min,  $P < 0.001$ ). Conclusions: It takes a median of just over 5 min to obtain three endobronchial biopsies in children, which we consider an acceptable increase in the duration of fiberoptic bronchoscopy for the purpose of research. **Pediatr Pulmonol.** 2009; 44:76–79. © 2008 Wiley-Liss, Inc.

**Key words:** fiberoptic bronchoscopy; child; endobronchial biopsy; bronchoalveolar lavage; airway remodeling.

## INTRODUCTION

Until recently, airway remodeling was considered to be a secondary phenomenon, developing late in the process of various chronic respiratory diseases as a consequence of repeated cycles of acute and acute on chronic inflammation. However, epidemiological studies have shown that at least in asthma, progressive decrease in lung function is already present in early childhood and tracks until adulthood, suggesting that remodeling may start early in life.<sup>1,2</sup> Pediatric studies have demonstrated that tissue remodeling is an early and consistent feature of chronic airway diseases including asthma, cystic fibrosis (CF) or non-CF bronchiectasis.<sup>3–6</sup> It has therefore been suggested that the preschool years may represent a window of opportunity before remodeling is established, during which an intervention might have long-term benefit.<sup>7,8</sup> Thus, identification of the early structural changes and understanding of the basic mechanisms driving airway remodeling may be central to future therapy and modification of the natural history of chronic airway disease.

Endobronchial biopsies are currently the gold standard of airway remodeling studies.<sup>9–11</sup> We have previously shown that the performance of endobronchial biopsy in children is safe and yields material of sufficient quality.<sup>12–15</sup> However, the extra-time needed for the procedure has

never been reported. The aim of the present study, which was carried out in the context of a larger study investigating the relationship between inflammation, infection and structural airway wall changes in CF,<sup>6,16</sup> was to evaluate the impact of performing endobronchial biopsy as a part of fiberoptic bronchoscopy on the length of the total procedure. We hypothesized that performance of endobronchial biopsy for the purpose of research would result in an acceptable increase in the duration of

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Grant sponsor: Swiss National Science Foundation, Grant number: 1172/05b (to NR); Grant sponsor: European Respiratory Society, Grant number: Fellowship No. 64 (to NR).

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Received 26 May 2008; Revised 23 August 2008; Accepted 23 August 2008.

DOI 10.1002/ppul.20949

Published online 9 December 2008 in Wiley InterScience (www.interscience.wiley.com).

fiberoptic bronchoscopy. Some of the results of this study have been previously reported in abstract form.<sup>17</sup>

## MATERIALS AND METHODS

### Subjects

Children who had a clinically indicated flexible bronchoscopy performed between May 2006 and February 2007, and in whom an attempt was made to take endobronchial biopsies as part of a research protocol<sup>6,16</sup> were prospectively enrolled. They either (i) had cystic fibrosis (CF), or (ii) were being investigated for recurrent wheeze or difficult asthma, or (iii) were being investigated for other chronic respiratory symptoms, with negative tests for CF and no history of wheeze or atopy. Diagnoses of CF and asthma were made according to standard criteria.<sup>18,19</sup> Children with known bleeding disorders or considered to be at-risk for complications by the consultant bronchoscopist or the anesthetist in charge of the procedure (e.g., risk of bronchospasm in an unstable child with brittle asthma) were not included in the research protocol. The study was approved by the local Research Ethics Committee. Biopsy was a routine part of the bronchoscopy in each of the patients included in the study, and informed consent for this research procedure had been obtained from the parents of all children.

### Flexible Bronchoscopy

All bronchoscopies were performed under general anesthesia as previously described.<sup>12</sup> Olympus BF-XP40 (2.8 mm external diameter), BF-3C20 or 3C40 (3.6 mm), BF-MP60 (4.0 mm videobronchoscope) or BF-P20D (4.9 mm) bronchoscopes (KeyMed, Southend-on-Sea, Essex, UK) were used, depending on the size of the child. Up to five biopsies were taken under direct vision from a standardized site (sub-segmental bronchi of the right lower lobe). Small re-usable forceps (FB-56D, oval cup with rat tooth jaw, KeyMed) were used with the 2.8 or 3.6 mm bronchoscope (both with a 1.2 mm working channel). Large single use forceps (FB-231D, oval cup standard, KeyMed) were used with the 4.0 or 4.9 mm

bronchoscope (both with a 2.2 mm working channel). A research assistant was in charge of liberating the tissue from the forceps into the fixation media. He immediately assessed visually the quality of the sample and informed the bronchoscopist about the number of macroscopically adequate pieces obtained so far, with the aim of obtaining at least three macroscopically adequate pieces per patient. Bronchoalveolar lavage (BAL) was performed using three aliquots of 1 ml/kg of room temperature 0.9% saline, instilled separately into the right middle lobe, unless otherwise indicated, and the return pooled. Without the knowledge of the bronchoscopist, time needed for inspection of the airways, BAL, sampling of three macroscopically adequate biopsies, teaching (e.g., manipulation of the bronchoscope by a specialist registrar), and other interventions (e.g., removal of plugs, video recording, sampling of additional biopsies) was recorded.

## RESULTS

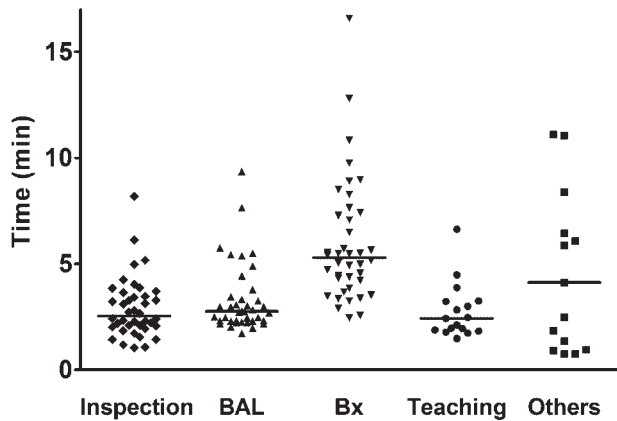
Fiberoptic bronchoscopy with endobronchial biopsy was performed in 40 children (median age 6 years, range 2 months to 16 years): 14 with CF, 6 investigated for recurrent wheeze or difficult asthma and 20 investigated because of other chronic respiratory symptoms (Table 1).

Median (range) bronchoscopy duration was 13.2 (8.2–29.5) min: 2.5 (1.0–8.2) for airway inspection, 2.8 (1.7–9.4) for BAL, 5.3 (2.5–16.6) for biopsy sampling, 2.4 (1.5–6.6) for teaching and 4.1 (0.8–18.5) for other interventions (Fig. 1). The median (range) duration needed for biopsy sampling was similar in disease groups: 6.0 min (3.4–16.6) for CF children, 4.9 min (3.3–7.3) for children with recurrent wheeze or difficult asthma and 4.8 min (2.5–12.8) for children investigated because of other chronic respiratory symptoms. Use of 2.0 mm biopsy forceps (with 4.0 and 4.9 mm bronchoscopes) rather than 1.0 mm (with 2.8 and 3.6 mm bronchoscopes) significantly reduced biopsy time: 4.6 (2.5–9.0) min versus 8.4 (4.4–16.6) min,  $P < 0.001$  (Mann–Whitney *U*-test).

Three macroscopically adequate biopsies were obtained in 33 (83%) children. In five cases, only two adequate

**TABLE 1—Subject Characteristics (n = 40)**

	CF (n = 14)	Asthma/wheeze (n = 6)	Chronic respiratory symptoms (n = 20)
Sex (female/male)	9:5	2:4	11:9
Age (year; range)	4.3 (0.6–10.7)	10.5 (1.5–16.3)	7.3 (0.2–15.2)
Indication for bronchoscopy (n)	Routine microbiological surveillance at the time of new CF diagnosis (7) Microbiological surveillance at the time of chest exacerbation (5) Microbiological surveillance at the time of line insertion (1) Reinflation of collapsed lobe (1)	Clinical assessment of difficult-to-control asthma (5) Clinical assessment of recurrent wheeze (1)	Investigation of chronic cough or recurrent chest infections (12) Microbiological surveillance at the time of chest exacerbation of known primary ciliary dyskinesia (2) Investigation of recurrent croup (3) Investigation of congenital stridor (2) Reinflation of collapsed lobe (1)



**Fig. 1.** Time needed during flexible bronchoscopy for airway inspection, bronchoalveolar lavage (BAL), sampling of three macroscopically adequate biopsies (Bx), teaching (e.g., driving of the bronchoscope by a specialist registrar), and other interventions (e.g., removal of plugs, video recording, sampling of additional biopsies; others) in 40 children. Horizontal bars show medians.

biopsies were obtained, in one case only one biopsy and in one case no biopsy at all. In these seven cases (four CF children and three children investigated for chronic respiratory symptoms), further biopsy sampling was not performed at the decision of the individual bronchoscopist, due to the procedure having lasted a considerable amount of time (8.9 (7.1–16.5) min).

After fixation in formal saline and staining with hematoxylin and eosin, 73 (66%) of 110 macroscopically adequate biopsies were considered evaluable for morphological analysis according to predefined criteria (i.e., (i) presence of epithelium, reticular basement membrane (RBM) and subepithelial tissue (no minimum requirement); (ii) good orientation; (iii) minimal crush, edema or blood within the biopsy<sup>15</sup>). All children in whom three macroscopically adequate biopsies were obtained had at least one biopsy considered as evaluable for morphological analysis. Success rate (i.e., obtaining at least one biopsy considered as evaluable for morphological analysis) was higher with the use of 2.0 mm biopsy forceps than with the use of 1.0 mm forceps: 96% (27/28) versus 58% (7/12),  $P = 0.006$  (Fisher's exact test). However, it did not differ between disease groups: 71% (10/14) for CF children, 100% (6/6) for children with recurrent wheeze or difficult asthma and 90% (18/20) for children investigated because of other chronic respiratory symptoms.

None of the 40 children experienced complications such as significant bleeding or pneumothorax during or after the procedure.

## DISCUSSION

This is the first study reporting the extra time needed to perform endobronchial biopsy in children during

bronchoscopy. Without the bronchoscopist being aware that the procedure was being timed, we found that the time needed to obtain three macroscopically adequate biopsies in children is just over 5 min, which compares with the time needed for airway inspection and bronchoalveolar lavage of approximately 2.5 min each. The duration needed for biopsy sampling was similar between patient groups but was affected significantly by the size of the forceps used, as was the rate of obtaining at least one biopsy considered as evaluable for morphological analysis. 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 faster and more efficient sampling.<sup>15</sup>

In most cases, three macroscopically adequate biopsies could be obtained within reasonable time, even in children as young as 2 months of age. However, as depicted in Figure 1, biopsy time exceeded 10 min in a few cases and even 15 min in one child. This was a 3-year-old CF child, in whom the sampling of biopsies was attempted with a 3.6-mm bronchoscope (with small forceps), and in whom large amounts of mucus obscured the view through the bronchoscope. Thus other factors than forceps size, such as presence of mucus may affect duration and efficiency of biopsy sampling.

We have previously shown that the probability of obtaining at least one evaluable biopsy in children is significantly increased if at least two biopsies are taken (80% success rate vs. 44% if only one biopsy is taken).<sup>15</sup> These findings are corroborated by the present study, in which we found only 2/3 of the biopsies taken were considered evaluable for morphological analysis. Furthermore, there is variability in structural characteristics between biopsies, and therefore multiple biopsies per subject should ideally be analyzed.<sup>9,20</sup> The sampling of multiple biopsies has, however, to be balanced against the risks and logistics of a longer period of general anesthesia. Based on the present study and on our experience, we would suggest researchers sample as many biopsies as possible (at least 2, ideally 5–7) within a reasonable amount of time which could be arbitrarily fixed as no longer than 10 min.

The use of endobronchial biopsies in children for the purpose of research has been critically discussed elsewhere.<sup>21–26</sup> Therefore, safety of the procedure and ethical considerations are not discussed in detail in the present study. As a note of caution, however, it has to be clearly

stated that these investigations need to be performed in a specialist center, by an experienced team of pediatric pulmonologists and anesthetists, in particular if biopsies are performed in children at higher risk for complications such as laryngo- or bronchospasm (e.g., children with severe asthma or infants with congenital stridor).

In conclusion, we show that it takes a median of just over 5 min to obtain three endobronchial biopsies in children, which we consider an acceptable increase in the duration of fiberoptic bronchoscopy for the purpose of research. Our data should allow parents to give more fully informed consent for this “added extra” procedure.

## ACKNOWLEDGMENTS

We thank Chloe Dunn, Bernie Ortega, Carmen Lacruz, Eleanor Singh, Gemma Moody and the staff of the Department Anesthesia, Royal Brompton Hospital, for their assistance with bronchoscopies and Andrew Nicholson and the Department of Pathology, Royal Brompton Hospital for their preparation of biopsy material. We also gratefully acknowledge the patients and families that agreed to take part in the study. Funding: Nicolas Regamey is the recipient of a European Respiratory Society Fellowship (Nr. 64) and of a grant of the Swiss National Science Foundation (Nr. 1172/05b).

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